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The Vascular Endothelium in Hypertension

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Abstract The vascular endothelium plays a fundamental role in the basal and dynamic regulation of the circulation. Thus, it has a crucial role in the pathogenesis of hypertension. A spectrum of vasoactive substances is synthesised in the endothelium; of these, nitric oxide (NO), prostacyclin (PGI_2) and endothelin (ET)-1 are the most important. There is a continuous basal release of NO determining the tone of peripheral blood vessels. Systemic inhibition of NO synthesis or scavenging of NO through oxidative stress causes an increase in arterial blood pressure. Also, the renin–angiotensin–aldosterone system has a major role in hypertension as it has a direct vasoconstrictor effect and important interactions with oxygen free radicals and NO. Prostacyclin, in contrast to NO, does not contribute to the maintenance of basal vascular tone of conduit arteries, but its effect on platelets is most important. ET acts as the natural counterpart to endothelium-derived NO and

has an arterial blood pressure-raising effect in man. Anti-hypertensive therapy lowers blood pressure and may influence these different mediators, thus influencing endothelial function. In summary, due to its position between the blood pressure and smooth muscle cells responsible for peripheral resistance, the endothelium is thought to be both victim and offender in arterial hypertension. The delicate balance of endothelium-derived factors is disturbed in hypertension. Specific anti-hypertensive and anti-oxidant treatment is able to restore this balance.

Keywords Endothelium · Hypertension · Nitric oxide · Endothelin · Oxidative stress

The vascular endothelium synthesises and releases a spectrum of vasoactive substances and therefore plays a fundamental role in the basal and dynamic regulation of the circulation (Lüscher and Vanhoutte 1990). Due to its strategic anatomical position, the endothelium is constantly exposed to the different risk factors for atherosclerosis.

1 Endothelial Vasoactive Substances

The endothelium—probably the largest and most extensive tissue in the body—forms a highly selective permeability barrier and is a continuous, uninterrupted, smooth, and non-thrombogenic surface. The endothelium synthesises and releases a broad spectrum of vasoactive substances (Fig. 1), including nitric oxide (NO), prostacyclin (PGI_2) and endothelin (ET)-1.

NO prevents leucocyte adhesion and migration into the arterial wall, smooth muscle cell proliferation, and platelet adhesion and aggregation, i.e. key events in the development of atherosclerosis (Bhagat et al. 1996; Bhagat and Vallance 1997; Boulanger and Lüscher 1990; Fichtlscherer et al. 2000; Hingorani et al. 2000; Ross 1999). NO, synthesised by NO synthase (NOS), is released from endothelial cells mainly in response to shear stress produced by blood flow (Anderson and Mark 1989; Furchgott and Zawadzki 1980; Joannides et al. 1995a, b; Palmer et al. 1988a, b; Rubanyi et al. 1986; Stamler et al. 1994; Vallance et al. 1989), leading to relaxation of vascular smooth muscle cells (Fig. 1; Palmer et al. 1988a). ET-1 acts as the natural counterpart to endothelium-derived NO (Lüscher et al. 1990). In addition to its arterial blood pressure-raising effect in man (Kiely et al. 1997; Vierhapper et al. 1990), ET-1 induces vascular and myocardial hypertrophy (Barton et al. 1998; Ito et al. 1991; Yang et al. 1999), which are independent risk factors for cardiovascular morbidity and mortality (Bots et al. 1997; Kannel et al. 1969; O'Leary et al. 1999). ET-1 stimulates the release of inflammatory mediators such as interleukin (IL)-1, IL-6 and IL-8, thereby antagonising the anti-inflammatory effects of NO. NO itself plays an important role in clinical systemic inflammatory syndromes when the inducible isoform of the NO-generating enzyme, iNOS, is activated.

2
Nitric Oxide in Hypertension

2.1
Biological Actions

NO, originally described as endothelium-derived relaxing factor (EDRF), is released from endothelial cells in response to shear stress produced by blood flow, and in response to activation of a variety of receptors (Fig. 1; Anderson and Mark 1989; Furchgott and Zawadzki 1980; Rubanyi et al. 1986; S. Moncada and E.A. Higgs, volume I). NO is a free radical gas—with a half-life in vivo of a few seconds—that is readily able to cross biological membranes (Furchgott and Zawadzki 1980; Palmer et al. 1987; Stamler et al. 1992). After diffusion from endothelial to vascular smooth muscle cells, NO increases intracellular cyclic guanosine monophosphate (cGMP) concentrations by activation of the enzyme guanylate cyclase, leading to relaxation of the smooth muscle cells (Palmer et al. 1988a).

NO is synthesised by NOS from L-arginine (Palmer et al. 1988a). The conversion from L-arginine to NO can be inhibited by false substrates for the NOS, e.g. by N^G-monomethyl-L-arginine (L-NMMA) (Palmer et al. 1988b). Since there is a continuous basal release of NO determining the tone of peripheral

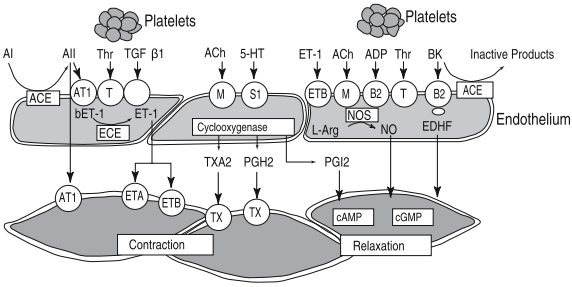

Fig. 1 Endothelium-derived vasoactive substances. Nitric oxide (NO) is released from endothelial cells in response to shear stress and to activation of a variety of receptors. NO exerts vasodilating and anti-proliferative effects on smooth muscle cells and inhibits thrombocyte aggregation and leucocyte adhesion. Endothelin-1 (ET-1) exerts its major vascular effects—vasoconstriction and cell proliferation—through activation of specific ET_A receptors on vascular smooth muscle cells. In contrast, endothelial ET_B receptors mediate vasodilatation via release of NO and prostacyclin. Additionally, ET_B receptors in the lung were shown to be a major pathway for the clearance of ET-1 from plasma. *ACE*, angiotensin-converting enzyme; *ACh*, acetylcholine; *AII*, angiotensin II; AT_1, angiotensin 1 receptor; *BK*, bradykinin; *COX*, cyclooxygenase; *ECE*, endothelin converting enzyme; *EDHF*, endothelium-derived hyperpolarising factor; ET_A and ET_B, endothelin A and B receptor; *ET-1*, endothelin-1; *L-Arg*, L-arginine; PGH_2, prostaglandin H_2; PGI_2, prostacyclin; *S*, serotoninergic receptor; *Thr*, thrombin; *T*, thromboxane receptor; TXA_2, thromboxane; *5-HT*, 5-hydroxytryptamine (serotonin). Modified from Lüscher and Noll (1997)

Table 1 Haemodynamic effects of NO synthase inhibition in healthy volunteers (modified after Spieker et al. 2000a)

	Baseline	L-NMMA	(mg/kg/min)
		0.3	1.0
SBP	134±7	152±5	150±3*
DBP	73±4	87±5	85±5 †
SVR	1114±124	1413±145*	1973±203‡
HR	67±4	70±6	63±6
CI	3.5±0.3	3.1±0.2*	2.3±0.2§
SVI	53±6	48±6	38±5†
CVP	4±0.7	3.6±0.4	4.3±0.05
B/min	23.1±3.5	14±4.5	18.6±5.5

*$p<0.05$, †$p<0.01$, ‡$p<0.001$, §$p<0.0001$, for each data point compared with baseline values
Abbreviations: B/min, sympathetic bursts per minute; CI, cardiac index ($l \cdot min^{-1} \cdot m^2$); CVP, central venous pressure (mmHg); DBP, diastolic blood pressure (mmHg); HR, heart rate (beats/min); L-NMMA, N^G-monomethyl-L-arginine; SBP, systolic blood pressure (mmHg); SVI, stroke volume index ($ml \cdot min^{-1} \cdot m^2$); SVR, systemic vascular resistance ($dyn \cdot s^{-1} cm^{-5}$)

blood vessels, systemic inhibition of NO synthesis causes an increase in arterial blood pressure (Anderson and Mark 1989; Palmer et al. 1988a, b; Rubanyi et al. 1986; Vallance et al. 1989). There are three types of NOS: two constitutive and one inducible isoform. The former, which are present in endothelial cells and neurons, are therefore called endothelial NOS (eNOS) and neuronal NOS (nNOS), respectively. The inducible form (iNOS) is an important inflammatory mediator expressed in macrophages, vascular smooth muscle and other cells in response to immunological stimuli (Palmer et al. 1992). NO has also anti-thrombogenic, anti-proliferative and leucocyte adhesion-inhibiting effects, and influences myocardial contractility (Anderson and Mark 1989; Joannides et al. 1995a, b; Vallance et al. 1989). The haemodynamic effects of pharmacological NO inhibition include an increase in blood pressure and a decrease in cardiac output (Table 1).

2.2 NO in Experimental Models of Hypertension

Endothelium-derived NO-mediated vascular relaxation is impaired in spontaneously hypertensive animals (Table 2; Diederich et al. 1990; Dohi et al. 1990; Lüscher and Vanhoutte 1986; Lüscher et al. 1986). Thus, the bioavailability of NO is reduced. Surprisingly, the NO pathway is paradoxically up-regulated in the resistance circulation and the heart of spontaneously hypertensive rats (SHR) (Kelm et al. 1992; Nava et al. 1998). Adult SHR possess a higher eNOS

Table 2 The nitric oxide (NO) pathway in selected experimental models of arterial hypertension

Animal model	Alteration in NO pathway
Spontaneously hypertensive rats (SHR)	Up-regulation
Stroke-prone SHR (SHRSP)	Up-regulation, but reduced bioavailability
Dahl salt-sensitive rats	Down-regulation
Two-kidney, one clip experimental hypertension (Goldblatt hypertension)	Impaired stimulated NO release, intact basal NO release
DOCA salt hypertensive rats	Impaired basal NO release

activity than their normotensive counterparts (Nava et al. 1995). Very young pre-hypertensive SHR have, in contrast, similar eNOS activity to young normotensive rats without a genetic background for hypertension, indicating that the increased activity of eNOS in adult SHR is indeed related to hypertension (Fig. 2). Moreover, the plasma concentrations of the oxidative product of NO metabolism, nitrate, are higher in hypertensive rats than in normotensive controls (Nava et al. 1998). These results indicate that the basal release of NO is increased in hypertensive rats.

Thus, it appears that in SHR there must be a factor blunting the haemodynamic effect of NO (Grunfeld et al. 1995). Indeed, NO production is increased in stroke-prone SHR (SHRSP), but bioavailability is reduced (McIntyre et al. 1997). Direct in situ measurement of NO release by a porphyrinic microsensor in SHRSP confirmed that hypertension is associated with increased NO

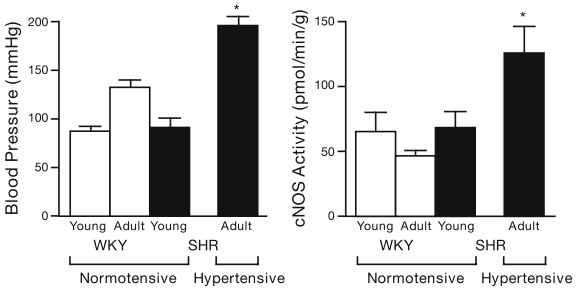

Fig. 2 Increased activity of constitutive nitric oxide synthase in cardiac endothelium of spontaneously hypertensive rats (SHR, *black bars*). Adult SHR possess a higher activity of constitutive nitric oxide synthase (NOS) than their normotensive counterparts (Wistar Kyoto rats, WKY; *open bars*). Very young pre-hypertensive SHR have, in contrast, lower constitutive NOS activity than the normotensive, indicating that the increased activity of NOS in adult SHR is indeed related to hypertension. Modified from Nava et al. (1995)

decomposition by superoxide anions, i.e. free oxygen radicals (Fig. 3; Tschudi et al. 1996). Nevertheless, a further increase of NO by inhibition of arginase, an enzyme which degrades L-arginine, the substrate of NO production by eNOS, has been shown to improve endothelial function and prevent the development of arterial hypertension in SHR (Demougeot et al. 2005).

In other models of hypertension—i.e. in Dahl salt-sensitive rats, in two-kidney, one clip experimental hypertension, and in desoxycorticosterone acetate (DOCA)-salt hypertensive rats—endothelium-dependent relaxation is also impaired (Table 2; Dohi et al. 1991; Hayakawa et al. 1993; Hirata et al. 1995; Lee et al. 1995; Lüscher et al. 1987a). In high-renin arterial hypertension such as the two-kidney, one-clip model there is impaired stimulated NO release but intact basal NO release (Artigues-Varin et al. 2002). Augmented NO production may serve as a counteracting system against the activation of the angiotensin receptor (AT_1) in this high-renin model of hypertension (Cervenka et al. 2002).

NO production by eNOS is reduced rather than up-regulated in Dahl salt-sensitive rats (Fig. 3; Hayakawa et al. 1993; Kakoki et al. 1999; Ni et al. 1999). L-Arginine, the substrate of NO production by eNOS, normalises blood pressure and simultaneously increases urinary excretion of nitrate, the degradation product of NO, in Dahl salt-sensitive rats (Chen and Sanders 1991, 1993; Chen et al. 1993; Hu and Manning 1995). Further mechanisms contribute to the pathogenesis of salt-sensitive hypertension. These include:

– Decreased expression of endothelial ET_B receptors, which mediate NO release (Hirata et al. 1995; Kakoki et al. 1999; Matsuoka et al. 1997)

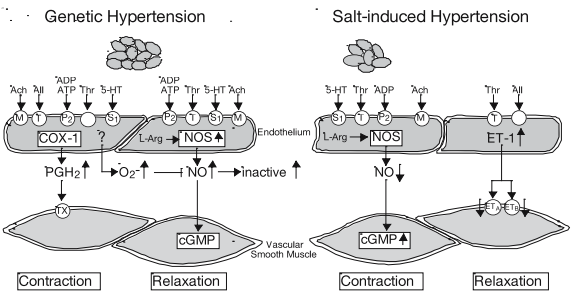

Fig. 3 Heterogeneity of endothelial dysfunction in experimental hypertension. In spontaneous hypertension (*left panel*) nitric oxide synthase (NOS) is upregulated and nitric oxide (NO) is inactivated by superoxide anions. In addition, the production of thromboxane (TXA_2) and prostaglandin H_2 (PGH_2) is increased. In salt-related hypertension (*right panel*), NO production is reduced and the endothelin (ET) system is upregulated. *ACE*, angiotensin-converting enzyme; *ACh*, acetylcholine; *AII*, angiotensin II; AT_1, angiotensin 1 receptor; *cGMP*, cyclic guanosine monophosphate; *COX*, cyclooxygenase; ET_A and ET_B, endothelin A and B receptor; *ET-1*, endothelin-1; *L-Arg*, L-arginine; *M*, muscarinergic receptor; O_2^-, superoxide anion; PGI_2, prostacyclin; *S*, serotoninergic receptor; *T*, thrombin receptor; *Thr*, thrombin; *TX*, thromboxane receptor; *5-HT*, 5-hydroxytryptamine (serotonin). Modified from Spieker et al. (2000b)

– Altered expression of the constitutive brain NOS (nNOS) as well as the iNOS isoform, possibly leading to alterations in renal sympathetic nervous activity and sodium handling (Deng and Rapp 1995; Ikeda et al. 1995; Rudd et al. 1999; Simchon et al. 1996)

Low functional levels of nNOS in the Dahl salt-sensitive rat may indeed contribute to its salt-sensitivity (Tan et al. 1999). In other low-renin models of hypertension, such as the DOCA salt-sensitive rat, there is augmented vascular superoxide production mediated via an ET_A/NADPH oxidase pathway (Li et al. 2003).

2.3 Nitric Oxide in Human Hypertension

There are several techniques for the assessment of NO bioavailability in man. Most often, flow-mediated vasodilatation (FMD) of the brachial artery—a marker of endothelial function—is assessed by high-resolution ultrasonography (Fig. 4). Alternatively, endothelium-dependent or -independent vasomotion in response to intra-arterially infused vasoactive substances is assessed using venous occlusion plethysmography. Among the most often used endothelium-dependent vasodilators are acetylcholine and serotonin (5-hydroxytryptamine). Sodium nitroprusside or nitroglycerin serves as an endothelium-independent vasodilator. Recently, new guidelines for assessment of endothelial function and dysfunction have been published, underlining the importance of standardised methods (Deanfield et al. 2005).

Endothelial dysfunction plays a crucial role in arterial hypertension (Brunner et al. 2005). Endothelium-dependent vasodilatation in response to acetylcholine is impaired in patients with arterial hypertension, both in the forearm circulation (Fig. 5; Creager and Roddy 1994; Hirooka et al. 1992; Linder et al. 1990; Panza et al. 1990, 1993a, b, c 1994; Taddei et al. 1994, 1995, 1997a) and in the coronary vascular bed (Egashira et al. 1995; Treasure et al. 1993). Especially in populations at low risk, endothelial function measured by FMD is related to the principal cardiovascular risk factors (Witte et al. 2005). There is a strong correlation between endothelium-dependent vasodilatation in the human forearm and coronary vascular beds (Anderson et al. 1995; Takase et al. 1998).

Basal NO activity is decreased in hypertensive patients (Calver et al. 1992). Furthermore, urinary excretion of the metabolic oxidation product of NO, ^{15}N nitrate, after administration of ^{15}N-labelled arginine (i.e. the substrate for the generation of NO) is reduced in hypertensive patients compared to normotensive controls (Fig. 5; Forte et al. 1997). Thus, whole-body NO production in patients with essential hypertension is diminished under basal conditions. In line with these findings, the vasoconstrictor response to L-NMMA, an inhibitor of NO synthesis, is significantly less in hypertensive patients compared

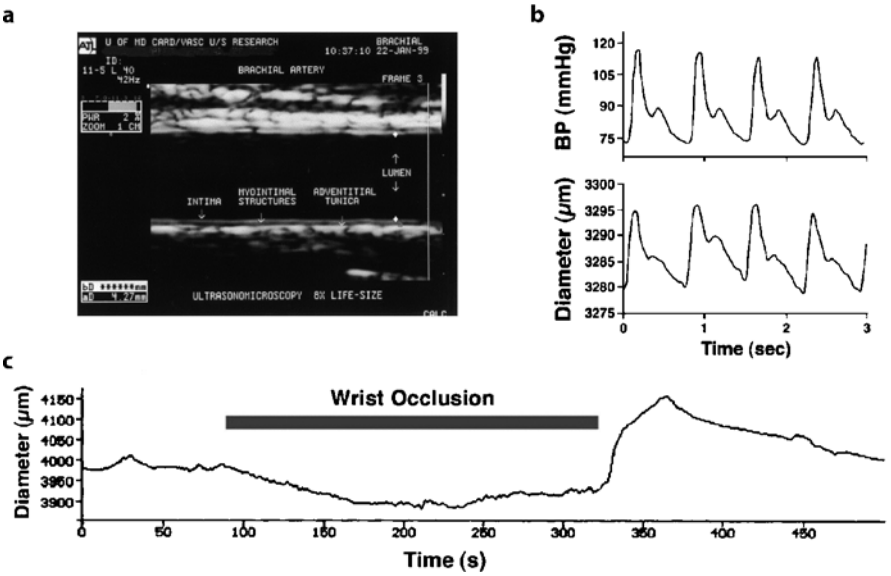

Fig. 4 Flow-mediated vasodilatation of the brachial artery is measured by high-resolution ultrasonography (**a**). With the use of echo-tracking, arterial diameter can be measured on a beat-to-beat basis (**b**). After establishing stable baseline conditions, flow-mediated vasodilatation is measured after release of a blood pressure cuff placed around the wrist and inflated to suprasystolic pressure for 5 min (**c**). The resulting hyperaemic blood flow to the hand after release of the wrist cuff leads to a more or less pronounced vasodilatation of the brachial artery, which is mediated by endothelium-derived nitric oxide (NO)

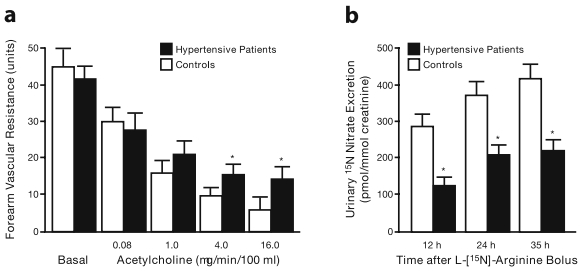

Fig. 5 a,b Endothelial dysfunction in arterial hypertension. **a** Patients with hypertension exhibit decreased endothelium-dependent vasodilatation in response to acetylcholine compared to normotensive controls. Modified from Linder et al. (1990). **b** Cumulative urinary excretion of ^{15}N nitrate after administration of ^{15}N-labelled arginine, i.e. the substrate for enzymatic production of NO. Urinary excretion of the metabolic oxidation product of NO, nitrate, is reduced in hypertensive patients compared to normotensive controls. These data show that whole-body NO production in patients with essential hypertension is diminished under basal conditions. Modified from Forte et al. (1997)

with normotensives, whereas there is no difference between hypertensives and normotensives in the response to noradrenaline, an endothelium-independent vasoconstrictor (Calver et al. 1992; Taddei et al. 1999a).

Normotensive offspring of hypertensive parents exhibit impaired endothelium-dependent vasodilatation to acetylcholine (Taddei et al. 1992). Vasoconstriction in response to an inhibitor of NO synthesis is also decreased in such subjects, indicating impaired basal synthesis of NO (McAllister et al. 1999). Thus, derangement of endothelial function in hypertension is likely to be caused in part by genetic factors, and is not just a consequence of elevated blood pressure (although the haemodynamic factor makes an important contribution) (Millgard and Lind 1998).

NO has a direct effect on vascular tone but, in addition, there is growing evidence that NO influences vascular tone by interaction with the central autonomic nervous system, resulting in sympatho-inhibitory effects in animals (Lewis et al. 1991) and in humans (Lepori et al. 1998). This indirect effect may also play an important role in the pathogenesis of arterial hypertension (Sartori et al. 2005).

3
Oxidative Stress in Hypertension

Oxidative stress plays an important role in the pathogenesis of hypertension (Fig. 6). Superoxide anion (O_2^-), an oxygen radical, can scavenge NO to form peroxynitrite ($ONOO^-$), effectively reducing the bioavailability of endothelium-derived NO (Fig. 7; Rubanyi and Vanhoutte 1986; Tschudi et al. 1996). In addition, O_2^- can act as a vasoconstrictor (Auch-Schwelk et al. 1989; Cosentino et al. 1994; Katusic et al. 1993; Katusic and Vanhoutte 1989). Nicotinamide adenine dinucleotide (NADH) dehydrogenase, a mitochondrial enzyme of the respiratory chain, seems to be a major source of O_2^- (Turrens and Boveris 1980). Expression of NAD(P)H oxidase in human coronary artery smooth muscle cells is up-regulated by pulsatile stretch, generating increased oxidative stress (Hishikawa et al. 1997). Another source of O_2^- is cyclooxygenase (COX) (Kontos et al. 1985). In contrast, xanthine oxidase, another generator of superoxide anions, does not appear to play a significant role in essential hypertension (Cardillo et al. 1997; Hishikawa et al. 1997).

Paradoxically, NOS (i.e. the NO generating enzyme) can also produce O_2^- (Cosentino et al. 1998; Kerr et al. 1999; Stroes et al. 1998). Production of O_2^- in SHRSP, an experimental model of genetic hypertension, can be prevented by NOS inhibition (Kerr et al. 1999). Administration of exogenous tetrahydrobiopterin (BH_4), an essential cofactor for NOS, can reduce excess O_2^- in the aorta of SHRSP (Kerr et al. 1999). In pre-hypertensive SHR, the calcium ionophore A23187 (a receptor-independent activator of NOS)-stimulated pro-

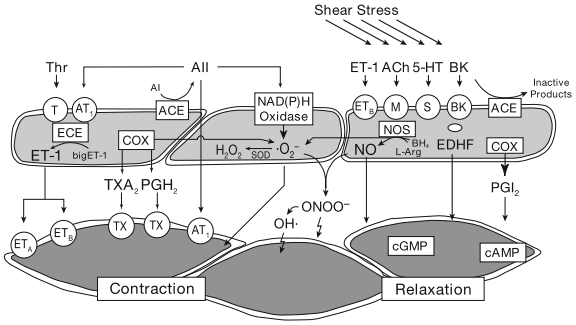

Fig. 6 Role of oxidative stress in the pathogenesis of endothelial dysfunction in hypertension. Superoxide anion, generated by angiotensin II-activated NAD(P)H oxidase, by dysfunctional NO synthase, and by cyclooxygenase, can scavenge the vasodilator NO to form the highly reactive peroxynitrite. Peroxynitrite can damage cell membranes and oxidise lipids. In addition, superoxide anion can act as a vasoconstrictor. *ACE*, angiotensin-converting enzyme; *ACh*, acetylcholine; *AII*, angiotensin II; AT_1, angiotensin 1 receptor; BH_4, tetrahydrobiopterin; *BK*, bradykinin; *COX*, cyclooxygenase; *ECE*, endothelin-converting enzyme; *EDHF*, endothelium-derived hyperpolarising factor; ET_A and ET_B, endothelin A and B receptor; *ET-1*, endothelin-1; H_2O_2, hydrogen peroxide; *L-Arg*, L-arginine; *NAD(P)H oxidase*, nicotinamide adenine dinucleotide oxidase; O_2^-, superoxide anion; *OH*, hydroxyl radical; $ONOO^-$, peroxynitrite; PGH_2, prostaglandin H_2; PGI_2, prostacyclin; *S*, serotoninergic receptor; *SOD*, superoxide dismutase; *Thr*, thrombin; *TXA*, thromboxane receptor; TXA_2, thromboxane; *5-HT*, 5-hydroxytryptamine (serotonin). Modified from Spieker et al. (2000b)

duction of O_2^- was significantly higher than in control rats. NO release was reduced in SHR aortas, with opposite results in the presence of exogenous BH_4. Thus, dysfunctional endothelial NOS may be a source of O_2^- in pre-

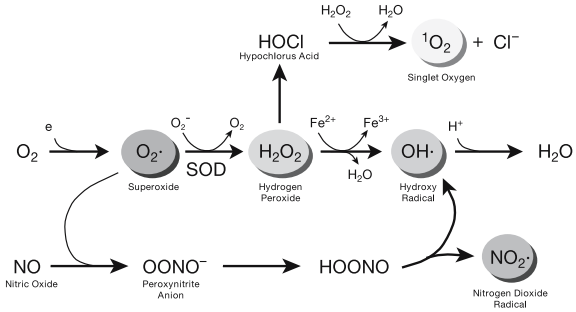

Fig. 7 Superoxide anion (O_2^-), an oxygen radical, is detoxified by superoxide dismutase (SOD), forming H_2O_2 which is further metabolised by catalase. However, the reaction between the two radicals O_2^- and NO is three times faster than the detoxification of O_2^- by SOD. Depending on the relative concentrations of NO and SOD, there may be a propensity for O_2^- to preferentially react with NO. O_2^- can scavenge NO to form peroxynitrite ($ONOO^-$), effectively reducing the bioavailability of endothelium-derived NO

hypertensive SHR and may contribute to the development of hypertension and its vascular complications (Cosentino et al. 1998; Jameson et al. 1993).

O_2^- is finally detoxified by superoxide dismutase (SOD), forming H_2O_2 which is further metabolised by catalase (Fridovich and Freeman 1986). However, the reaction between the two radicals O_2^- and NO is three times faster than the detoxification of O_2^- by SOD (Thomson et al. 1995). Depending on the relative concentrations of NO and SOD, there may be a propensity for O_2^- to react preferentially with NO, resulting in decreased bioavailability of NO. In SHR aortas, SOD (Sekiguchi et al. 2004) or the oral administration of potent anti-oxidants such as flavonoids (Machha and Mustafa 2005) is able to improve endothelium-dependent relaxation. This underlines the importance of scavenging free oxygen radicals, as the imbalance between oxidative stress and the anti-oxidant defence mechanism is considered a major factor in the development of hypertension.

The gene for cytosolic SOD (i.e. SOD1) is located on the 21q22.1 region of chromosome 21 (Levanon et al. 1985). Patients with Down's syndrome (trisomy 21) have an extra copy of the SOD gene. Because of gene dosage excess, their SOD activity is 50% greater than in the diploid population, leading to reduced O_2^- levels (De La Torre et al. 1996). Patients with Down's syndrome have lower blood pressure levels, indicating a major role for O_2^- in the regulation of arterial blood pressure. Furthermore, the normal age-associated increase of blood pressure is absent in patients with Down's syndrome (Morrison et al. 1996).

3.1 The Renin–Angiotensin–Aldosterone System

The renin–angiotensin system plays a major role in hypertension (Fig. 1; Goldblatt et al. 1934; C. Dimitropoulou et al., volume I). Apart from the direct vasoconstrictor effects of angiotensin II (ANG II), there are important interactions between ANG II, oxygen radicals, and NO. Indeed, ANG II stimulates the generation of O_2^- by increasing the expression of the NAD(P)H oxidase gene (*p22phox* and others) and increasing the activity of NAD(P)H oxidase (Fukui et al. 1997; Laursen et al. 1997; Rajagopalan et al. 1996; Zafari et al. 1998). The vasoconstrictor effect of ANG II is enhanced in the absence of NO, and diminished during co-infusion of anti-oxidant vitamin C (Dijkhorst-Oei et al. 1999). Thus, the vasoconstrictor effect of ANG II is modulated by reactive oxygen species, mainly O_2^-, and their interaction with endothelium-derived NO (Fig. 6). In addition, ANG II-induced oxidative stress results in the activation of several pro-inflammatory transcription factors (Cheng et al. 2005). Statins, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, ameliorate ANG II-induced hypertension and vascular inflammatory response independently of cholesterol reduction (Dechend et al. 2001). Inhibition of NO synthesis by oral L-NAME increases the activity of the renin–angiotensin

system and ANG II concentration (Vandermeersch et al. 2003). Studies suggest that the protective effects of angiotensin-converting enzyme inhibitors on the ANG II-induced inflammatory response are linked to the improvement of NO bioavailability (Chen et al. 2003). Furthermore, ANG II increases the production of ET in the blood vessel wall, which exerts vasoconstriction and induces proliferation of the vascular smooth muscle cells (Moreau et al. 1997).

4 Prostaglandins in Hypertension

PGI_2 is another endothelium-derived relaxing factor that is released in response to shear stress (Fig. 1; Koller and Kaley 1990; Okahara et al. 1998; Pohl et al. 1986; Rubanyi et al. 1986). PGI_2 is synthesised by COX from arachidonic acid (Moncada et al. 1976). PGI_2 increases intracellular cyclic adenosine monophosphate (cAMP) in smooth muscle cells and platelets. In contrast to NO, PGI_2 does not contribute to the maintenance of basal vascular tone of large conduit arteries (Joannides et al. 1995a). Instead, its platelet inhibitory effects are most important. The synergistic effect of PGI_2 and NO enhances the anti-platelet activity (Radomski et al. 1987).

Depending on the animal model of hypertension and the vascular bed, endothelium-dependent contractions to acetylcholine, a muscarinic receptor-dependent stimulator of NO synthesis, have been documented (Fig. 3). Since this response is inhibited by COX inhibitors and thromboxane receptor antagonists, the most likely contractile factors are thromboxane A_2 and prostaglandin H_2 (Küng and Lüscher 1995; Noll et al. 1997).

Interactions between COX products and NO have been demonstrated (Yang et al. 1991). Celecoxib, a selective COX-2 inhibitor, was able to improve endothelial function and reduce oxidative stress (Hermann et al. 2003) as well to reduce cellular inflammation in a model of salt-sensitive hypertensive rats (Hermann et al. 2005). In humans, selective inhibition of COX-2 by celecoxib lowers C-reactive protein levels and improves endothelial function in patients with coronary artery disease (Chenevard et al. 2003). Short- (3 h) and long-term (1 week) inhibition of COX-2 by celecoxib restores endothelial function in hypertensive patients (Widlansky et al. 2003), whereas rofecoxib has no effect (Title et al. 2003; Verma et al. 2001). In hypertensive patients, indomethacin, a COX inhibitor, significantly increased the response to acetylcholine, an effect that could be blocked by co-infusion of L-NMMA, an inhibitor of NO synthesis (Taddei et al. 1997b). Therefore, COX inhibition restores NO-mediated vasodilatation in essential hypertension, suggesting that COX-dependent substances can impair NO bioavailability. COX is indeed a source of the NO scavenger O_2^- (Kontos et al. 1985).

5
Endothelium-Derived Hyperpolarising Factor

Inhibitors of the L-arginine pathway do not prevent all endothelium-dependent relaxations (Richard et al. 1990). Since under these conditions vascular smooth muscle cells become hyperpolarised, an endothelium-dependent hyperpolarising factor (EDHF) of unknown chemical structure has been proposed (Fig. 1; Taylor and Weston 1988; Vanhoutte 1987). There is evidence that a calcium-dependent potassium channel on endothelial or smooth muscle cells is important in mediating endothelium-dependent hyperpolarisation, a mechanism that is impaired in arterial hypertension (Edwards et al. 1998; Fujii et al. 1992; Van de Voorde et al. 1992). Endothelium-dependent hyperpolarisation may also be involved in the compensation for the impaired NO system in patients with essential hypertension (Taddei et al. 1999b; Takase et al. 1996).

As EDHF remains unidentified, its involvement in regulating vascular reactivity is defined as the response that persists in the presence of combined inhibition of NO and PGI_2 synthesis. The relative contribution of the mediators to endothelium-dependent dilatation (NO, prostacyclin and EDHF) is inversely related to vessel calibre. NO- and PGI_2-mediated responses are more important in conduit vessels, whereas EDHF is more prominent in resistance arteries (Shimokawa et al. 1996).

A recent study in $eNOS^{-/-}$ and $COX^{-/-}$ mice shows that EDHF is the predominant endothelium-derived relaxing factor in female mice, whereas NO and PGI_2 are predominant mediators in male mice (Scotland et al. 2005). The disruption of both eNOS and COX genes resulted in elevated blood pressure in male mice, whereas the female mice were protected against hypertension, indicating that EDHF may contribute to the lower incidence of cardiovascular disease in pre-menopausal women (Scotland et al. 2005).

6
The Endothelin System

Over a decade ago, a novel vasoconstrictor peptide synthesised by vascular endothelial cells was identified (Hickey et al. 1985; Yanagisawa et al. 1988; see A.P.Davenport and J.J. Maguire, volume I). The ET family consists of three closely related peptides—ET-1, ET-2, and ET-3—which are converted by ET-converting enzymes (ECE) from "big endothelins" originating from large pre-proendothelin peptides cleaved by endopeptidases (Ikegawa et al. 1990; Ohnaka et al. 1993; Rossi et al. 1995; Shimada et al. 1994; Takahashi et al. 1993). The ET peptides are not only synthesised in vascular endothelial and smooth muscle cells, but also in neural, renal, pulmonal and some circulatory cells holding the genes for ETs (Inoue et al. 1989a, b). The chemical structure of the ETs is closely related to neurotoxins (sarafotoxins) produced by scorpions and snakes (Fleminger et al. 1989; Kloog et al. 1988). Factors modulating the

expression of ET-1 are shear stress, adrenaline, ANG II, thrombin, inflammatory cytokines (tumour necrosis factor α, interleukin-1 and -2), transforming growth factor β and hypoxia (Barton et al. 1997; Boulanger and Lüscher 1990; Boulanger et al. 1992; Dohi et al. 1992; Hieda and Gomez-Sanchez 1990; Kanse et al. 1991; Kohno et al. 1989; Kourembanas et al. 1991; Miyamori et al. 1991; Ohta et al. 1990; Shirakami et al. 1991; Woods et al. 1998; Yoshizumi et al. 1989). ET-1 is metabolised by a neutral endopeptidase that also cleaves natriuretic peptides (Abassi et al. 1992, 1993).

Imbalance of endothelium-derived relaxing and contracting substances disturbs the normal function of the vascular endothelium (Lüscher 1990; Lüscher and Vanhoutte 1990). ET acts as the natural counterpart to endothelium-derived NO (Fig. 1), which exerts vasodilating, anti-thrombotic, and anti-proliferative effects, and inhibits leucocyte adhesion to the vascular wall (Boulanger and Lüscher 1990). In addition to its arterial blood pressure-raising effect in man (Kiely et al. 1997; Vierhapper et al. 1990), ET-1 induces both vascular and myocardial hypertrophy (Barton et al. 1998; Ito et al. 1991; Yang et al. 1999), which are independent risk factors for cardiovascular morbidity and mortality (Bots et al. 1997; Kannel et al. 1969; O'Leary et al. 1999). Indeed, in patients with essential hypertension, carotid wall thickening and left ventricular mass correlate with reduced endothelium-dependent vasodilatation (Ghiadoni et al. 1998; Perticone et al. 1999a).

ET-1 has a paracrine rather than an endocrine mode of action, which is reflected by plasma levels of ET-1 in the picomolar range (Sorensen 1991; Wagner et al. 1992). Infusion of an ET receptor antagonist into the brachial artery or systemically in healthy humans leads to vasodilatation, indicating a role of ET-1 in the maintenance of basal vascular tone (Haynes and Webb 1994; Haynes et al. 1996). When ET-1 itself is infused, vasoconstriction follows a brief phase of vasodilatation, which may be explained by relaxation of smooth muscle cells caused by ET_B receptor-mediated release of the vasodilators NO and PGI_2 (Fig. 1). In addition, ET-1 may exert effects on the central and autonomic nervous systems and alter baroreflex function (Chapleau et al. 1992; Donckier et al. 1991; Gardiner et al. 1990; Kannan et al. 1994; Knuepfer et al. 1989; Lysko et al. 1991; Mosqueda-Garcia et al. 1998; Nakamoto et al. 1991; Nambi et al. 1990; van den Buuse and Itoh 1993; Yang et al. 1990a, b). In the kidney, sodium re-absorption is modulated (Sorensen et al. 1994) and aldosterone secretion is regulated by ET-1 (Fig. 8; Rossi et al. 2003).

6.1 The Endothelin System in Hypertension

The ET system is activated in several but not all animal models of arterial hypertension (Barton et al. 1998; Doucet et al. 1996; Hocher et al. 1995, 1996, 1999; Lariviere et al. 1993a, b, 1995; Li et al. 1994; Miyauchi et al. 1989; Schiffrin et al. 1995a). Correspondingly, ET plasma levels have been reported to be elevated

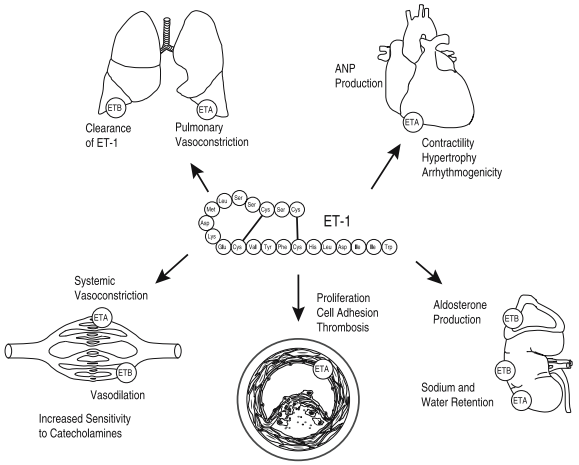

Fig. 8 Pathophysiological role of endothelin (ET)-1. In the heart, ET-1 contributes to contractility. In addition to its vasoconstrictor effects in the systemic and pulmonary circulation, ET-1 leads to hypertrophy of myocardial and smooth muscle cells. The pulmonary circulation is an important source of ET-1, but is also involved in the clearance of ET-1. In the kidney, ET-1 regulates sodium and water excretion. Modified from Spieker et al. (2001)

in certain patients with essential hypertension (Saito et al. 1990), but this observation is controversial (Miyauchi et al. 1992; Taddei et al. 1999a). The causal role of ET-1 in the pathogenesis of hypertension thus remains unclear (Haynes et al. 1998). As ET has pro-inflammatory, hypertrophic and pro-fibrotic properties in the heart, kidney and blood vessels, it seems to play a predominant role in mediating complications of hypertension (Schiffrin 2005).

Because most ET-1 synthesised in endothelial cells is secreted abluminally, it might attain a higher concentration in the vessel wall than in the plasma. Indeed, significant correlations have been found between the amount of immunoreactive ET-1 in the tunica media and (1) blood pressure, (2) total serum cholesterol and (3) the number of atherosclerotic sites (Rossi et al. 1999). In blood vessels of healthy controls, ET-1 was detectable almost exclusively in endothelial cells, whereas in patients with coronary artery disease, arterial hypertension or both, sizeable amounts of ET-1 were detectable in the tunica media of different types of arteries (Rossi et al. 1999). Furthermore, there is evidence that certain gene polymorphisms of ET-1 and ET receptors could be associated with blood pressure levels (Nicaud et al. 1999; Sharma et al. 1999; Stevens and Brown 1995). Even at very low concentrations of ET-1, interactions between ET-1 and adrenergic mediators lead to enhanced vasoconstriction (Fig. 9; Yang et al. 1990b).

Moreover, in hypertensive patients, intra-arterial infusion of various $ET_{A/B}$ receptor antagonists caused significantly greater vasodilatation than in normotensive subjects (Fig. 10; Cardillo et al. 1999, 2004; Taddei et al. 1999a). However, these findings remain controversial (Ferro et al. 2002; Nohria et al.

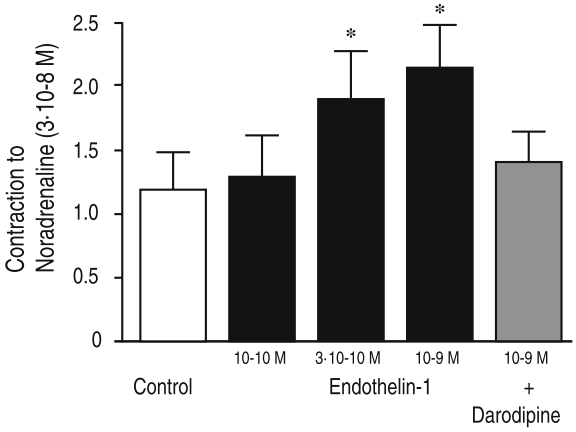

Fig. 9 Threshold concentrations of endothelin-1 potentiate contractions to noradrenaline in human arteries. In mammary artery rings, the contractions to noradrenaline were potentiated by threshold and low concentrations of endothelin-1. The calcium antagonist darodipine prevented the potentiation of the response to noradrenaline evoked by endothelin-1. Modified from Yang et al. (1990b)

2003). If plasma levels of ET-1 are similar in normotensive and hypertensive patients, then increased sensitivity to endogenous ET-1 must be postulated. Indeed, sensitivity to endogenous and exogenous ET-1 is increased in hypertensive patients (Nohria et al. 2003; Taddei et al. 1999a). One of the major functional consequences is impaired exercise-induced vasodilatation in hypertensive subjects, both in the coronary and the peripheral circulation (Fig. 11; Frielingsdorf et al. 1996; Linder et al. 1990; Nohria et al. 2003; Panza et al. 1990). Decreased bioavailability of NO may be involved in this phenomenon, since NO antagonises some of the effects of ET-1.

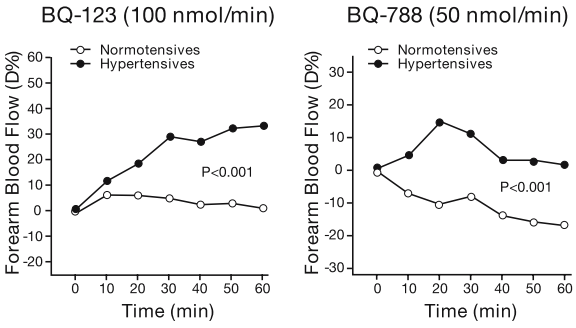

Fig. 10 Forearm blood flow responses to intra-arterial infusion of the selective ET_A receptor antagonist BQ-123 (100 nmol/min), and the ET_B receptor antagonist BQ-788 (50 nmol/min) in hypertensive patients and normotensive controls. The vasodilator response to endothelin antagonism is significantly enhanced in hypertensives. Modified from Cardillo et al. (1999)

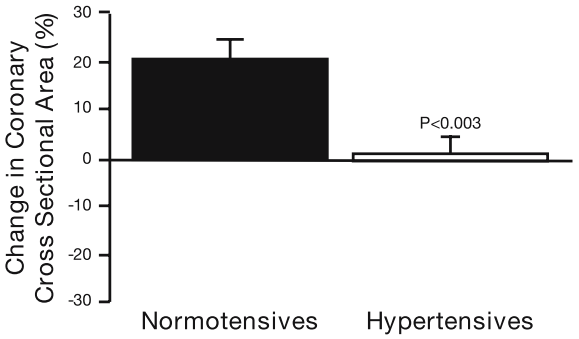

Fig. 11 Coronary luminal area change during exercise in hypertensive patients and normotensive control subjects. Exercise-induced coronary vasodilatation is impaired in hypertensives. Modified from Frielingsdorf et al. (1996)

7
Effects of Anti-hypertensive Therapy on the Vascular Endothelium in Hypertensive Patients

In hypertensive animals, most classes of anti-hypertensive drugs (e.g. calcium-channel blockers, ACE-inhibitors, AT_1 receptor antagonists) improve endothelium-dependent vasodilatation (Boulanger et al. 1994; d'Uscio et al. 1998; Dohi et al. 1994; Lüscher et al. 1987b; Maeso et al. 1998; Rodrigo et al. 1997; Takase et al. 1996; Tschudi et al. 1994). Surprisingly and in contrast to animal experiments, anti-hypertensive therapy cannot consistently restore impaired endothelium-dependent vasodilatation in patients with arterial hypertension (Creager and Roddy 1994; Hirooka et al. 1992; Linder et al. 1990; Panza et al. 1990, 1993a, b, c, 1994, 1995; Taddei et al. 1994, 1995, 1997a). However, depending on the anti-hypertensive drug and its pharmacological profile, improvements in endothelium-dependent vasodilatation can be achieved (Table 3; Creager et al. 1992; Dawes et al. 1999; Ghiadoni et al. 2000, 2003; Hirooka et al. 1992; Lyons et al. 1994; Millgard et al. 1998; Millgard and Lind 1998; Panza et al. 1993c; Perticone et al. 1999b; Schiffrin and Deng 1996; Schiffrin et al. 1995a; Schiffrin et al. 1995b; Sudano et al. 1998; Taddei et al. 1994, 1997c, 1998a; Yavuz et al. 2003). The multifactorial aetiology of essential hypertension as well as the duration of blood pressure elevation may explain certain inconsistent results of different investigators (Cockcroft et al. 1994; Perticone et al. 1998).

Several calcium channel blocking agents have been successful in improving endothelial function in human hypertension (Table 3). The anti-oxidative properties of an anti-hypertensive drug are important, since oxidative stress plays a central role in the pathophysiology of human hypertension. The endothelial function of patients with hypertension is improved by acute administration of ascorbic acid, an anti-oxidant vitamin, which protects against the decomposition of NO by O_2^- (Taddei et al. 1998b). Scavenging of reactive oxygen species by

Table 3 Effect of antihypertensive therapy on endothelial function in patients with arterial hypertension

Reference	Antihypertensive therapy	Duration of treatment	NO-release agonist/ antagonist	Improvement in endothelium-dependent vasomotion
	ACE inhibitors			
Hirooka et al. 1992	Captopril	Acute	ACh	Yes
Creager et al. 1992	Captopril	7–8 weeks	MCh	No
	Enalapril	7–8 weeks	MCh	No
Taddei et al. 1998a	Lisinopril	Acute	ACh	No
			Bk	Yes
		1 and	ACh	No
		12 month	Bk	Yes
Lyons et al. 1994	Enalapril	6 weeks	L-NMMA	Yes
Millgard et al. 1998	Captopril	Acute	MCh	Yes
		3 months	MCh	Yes
Schiffrin et al. 1995b	Cilazapril	1 and 2 years	ACh	Yes
Yavuz et al. 2003	Enalapril	6 months	FMD	Yes
Ghiadoni et al. 2003	Perindopril	6 months	FMD	Yes
	ANG II antagonist			
Ghiadoni et al. 2000	Candesartan	2 months	ACh	No
		12 months	ACh	Yes*
Bragulat et al. 2003	Irbesartan	6 months	ACh	Yes*
Yavuz et al. 2003	Losartan	6 months	FMD	No
Ghiadoni et al. 2003	Telmisartan	6 months	FMD	No
	β-Blocker			
Schiffrin and Deng 1996	Atenolol	2 years	ACh	No
Dawes et al. 1999	Nebivolol	Acute	L-NMMA	Yes
Ghiadoni et al. 2003	Nebivolol	6 months	FMD	No
Ghiadoni et al. 2003	Atenolol	6 months	FMD	No

Table 3 (continued)

Reference	Antihypertensive therapy	Duration of treatment	NO-release agonist/ antagonist	Improvement in endothelium-dependent vasomotion
	Ca antagonists			
Hirooka et al. 1992	Nifedipine	Acute	ACh	No
Millgard et al. 1998	Nifedipine	Acute	MCh	No
Sudano et al. 1998	Nifedipine	6 months	ACh	Yes
Schiffrin and Deng 1996	Nifedipine	Chronic	ACh	Yes
Ghiadoni et al. 2003	Nifedipine	6 months	FMD	No
Taddei et al. 1997c	Lacidipine	2 and 8 month	ACh and Bk	Yes
Lyons et al. 1994	Amlodipine	6 weeks	L-NMMA	Yes
Perticone et al. 1999b	Isradipine	2 and 6 month	ACh	Yes
Ghiadoni et al. 2003	Amlodipine	6 months	FMD	No
	Other			
Panza et al. 1993c	Various (diuretics, verapamil, β-blockers, clonidine, α-methyldopa)	Chronic vs 2 weeks withdrawal	ACh ACh	No No
Taddei et al. 1994	Potassium	Acute	ACh	Yes

Abbreviations: ANG II, angiotensin II; ACE, angiotensin converting enzyme; ACh, acetylcholine; Bk, bradykinin; Ca, calcium; FMD, flow-mediated vasodilatation; L-NMMA, N^G-monomethyl-L-arginine; MCh, methacholine; NO, nitric oxide *This effect was paralleled by an enhanced endothelium-independent vasodilatation to sodium nitroprusside

anti-oxidants may become an important therapeutic strategy (Nakazono et al. 1991; Tschudi et al. 1996), since chronic treatment with vitamin C is in fact able to lower blood pressure in patients with hypertension (Duffy et al. 1999).

Treatment with candesartan, an AT_1 receptor antagonist, reduced the vasodilator response to the mixed $ET_{A/B}$ receptor antagonist TAK-044 that was initially more pronounced in hypertensive patients than in normotensive con-

trols (Ghiadoni et al. 2000). This was paralleled by a reduction in circulating plasma ET-1 levels. Furthermore, the impaired vasoconstrictor response to L-NMMA in hypertensives was augmented by anti-hypertensive treatment. Thus, the ANG II receptor blocker candesartan improves the basal release of NO and reduces vasoconstriction to endogenous ET-1 in the forearm of hypertensive patients. Irbesartan, another AT_1 receptor antagonist, has also been investigated in hypertensive patients. Long-term irbesartan treatment enhanced both endothelium-dependent and -independent vascular vasodilatation responses. In addition, irbesartan restored the vasoconstrictor capacity of L-NMMA, suggesting a direct effect on tonic NO release, and decreased ET-1 production (Bragulat et al. 2003). However, other AT_1 receptor antagonists such as telmisartan and losartan did not improve endothelium-dependent vasodilatation in hypertensive patients (Ghiadoni et al. 2003; Yavuz et al. 2003).

Interestingly, infusion of nebivolol, but not other β-blockers, intra-arterially in the forearm of healthy subjects is associated with an increase in forearm blood flow (Cockcroft et al. 1995). The increase in forearm blood flow achieved by nebivolol can be prevented by co-infusion of L-NMMA. Similar results have been obtained in the human venous circulation (Bowman et al. 1994). This strongly suggests that nebivolol stimulates the formation of NO in the vasculature and may therefore have an interesting haemodynamic profile which—unlike other β-blockers—leads to peripheral vasodilatation in addition to the classical β-blocking effects on the sympathetic nervous system, heart rate and cardiac contractility (Van Nueten and De Cree 1998; Wallin et al. 1984). Indeed, nebivolol also causes NO-dependent vasodilatation in hypertensive patients (Dawes et al. 1999). However, this favourable effect did not last during chronic treatment (6 months) with this new type of β_1-blocker (Ghiadoni et al. 2003).

The effects of newer anti-hypertensive agents—e.g. ET receptor antagonists, ECE inhibitors, and inhibitors of neutral endopeptidases cleaving natriuretic peptides—on endothelial function in hypertension are awaited.

8 Conclusions

The vascular endothelium, synthesising and releasing vasoactive substances, plays a crucial role in the pathogenesis of hypertension. Due to its position between the blood pressure and smooth muscle cells responsible for peripheral resistance, the endothelium is thought to be both victim and offender in arterial hypertension. The delicate balance of endothelium-derived factors, which is disturbed in hypertension, can be restored by specific anti-hypertensive and anti-oxidant treatment.

References

Abassi ZA, Tate JE, Golomb E, Keiser HR (1992) Role of neutral endopeptidase in the metabolism of endothelin. Hypertension 20:89–95

Abassi ZA, Golomb E, Bridenbaugh R, Keiser HR (1993) Metabolism of endothelin-1 and big endothelin-1 by recombinant neutral endopeptidase EC.3.4.24.11. Br J Pharmacol 109:1024–1028

Anderson EA, Mark AL (1989) Flow-mediated and reflex changes in large peripheral artery tone in humans. Circulation 79:93–100

Anderson TJ, Uehata A, Gerhard MD, Meredith IT, Knab S, Delagrage D, Lieberman EH, Ganz P, Creager MA, Yeung AC, Selwyn AP (1995) Close relation of endothelial function in the human coronary and peripheral circulation. J Am Coll Cardiol 26:1235–1241

Artigues-Varin C, Richard V, Renet S, Henry JP, Thuillez C (2002) Lack of impairment of nitric oxide-mediated responses in a rat model of high-renin hypertension. Clin Exp Pharmacol Physiol 29:26–31

Auch-Schwelk W, Katusic ZS, Vanhoutte PM (1989) Contractions to oxygen-derived free radicals are augmented in aorta of the spontaneously hypertensive rat. Hypertension 13:859–864

Barton M, Shaw S, d'Uscio LV, Moreau P, Lüscher TF (1997) Angiotensin II increases vascular and renal endothelin-1 and functional endothelin converting enzyme activity in vivo: role of ETA receptors for endothelin regulation. Biochem Biophys Res Commun 238: 861–865

Barton M, d'Uscio LV, Shaw S, Meyer P, Moreau P, Lüscher TF (1998) ET(A) receptor blockade prevents increased tissue endothelin-1, vascular hypertrophy, and endothelial dysfunction in salt-sensitive hypertension. Hypertension 31:499–504

Bhagat K, Vallance P (1997) Inflammatory cytokines impair endothelium-dependent dilatation in human veins in vivo. Circulation 96:3042–3047

Bhagat K, Moss R, Collier J, Vallance P (1996) Endothelial "stunning" following a brief exposure to endotoxin: a mechanism to link infection and infarction? Cardiovasc Res 32:822–829

Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE (1997) Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 96:1432–1437

Boulanger C, Lüscher TF (1990) Release of endothelin from the porcine aorta. Inhibition of endothelium-derived nitric oxide. J Clin Invest 85:587–590

Boulanger CM, Tanner FC, Bea ML, Hahn AW, Werner A, Lüscher TF (1992) Oxidized low density lipoproteins induce mRNA expression and release of endothelin from human and porcine endothelium. Circ Res 70:1191–1197

Boulanger CM, Desta B, Clozel JP, Vanhoutte PM (1994) Chronic treatment with the CA2+ channel inhibitor RO 40–5967 potentiates endothelium-dependent relaxations in the aorta of the hypertensive salt sensitive Dahl rat. Blood Press 3:193–196

Bowman AJ, Chen CP, Ford GA (1994) Nitric oxide mediated venodilator effects of nebivolol. Br J Clin Pharmacol 38:199–204

Bragulat E, Larrousse M, Coca A, de la Sierra A (2003) Effect of long-term irbesartan treatment on endothelium-dependent vasodilation in essential hypertensive patients. Br J Biomed Sci 60:191–196

Brunner H, Cockcroft JR, Deanfield J, Donald A, Ferrannini E, Halcox J, Kiowski W, Lüscher TF, Mancia G, Natali A, Oliver JJ, Pessina AC, Rizzoni D, Rossi GP, Salvetti A, Spieker LE, Taddei S, Webb DJ (2005) Endothelial function and dysfunction. Part II. Association with cardiovascular risk factors and diseases. A statement by the Working Group on Endothelins and Endothelial Factors of the European Society of Hypertension. J Hypertens 23:233–246

Calver A, Collier J, Moncada S, Vallance P (1992) Effect of local intra-arterial N^G-monomethyl-L-arginine in patients with hypertension: the nitric oxide dilator mechanism appears abnormal. J Hypertens 10:1025–1031

Cardillo C, Kilcoyne CM, Cannon RO 3rd, Quyyumi AA, Panza JA (1997) Xanthine oxidase inhibition with oxypurinol improves endothelial vasodilator function in hypercholesterolemic but not in hypertensive patients. Hypertension 30:57–63

Cardillo C, Kilcoyne CM, Waclawiw M, Cannon RO 3rd, Panza JA (1999) Role of endothelin in the increased vascular tone of patients with essential hypertension. Hypertension 33:753–758

Cardillo C, Campia U, Iantorno M, Panza JA (2004) Enhanced vascular activity of endogenous endothelin-1 in obese hypertensive patients. Hypertension 43:36–40

Cervenka L, Horacek V, Vaneckova I, Hubacek JA, Oliverio MI, Coffman TM, Navar LG (2002) Essential role of AT1A receptor in the development of 2K1C hypertension. Hypertension 40:735–741

Chapleau MW, Hajduczok G, Abboud FM (1992) Suppression of baroreceptor discharge by endothelin at high carotid sinus pressure. Am J Physiol 263:R103–R108

Chen PY, Sanders PW (1991) L-Arginine abrogates salt-sensitive hypertension in Dahl/Rapp rats. J Clin Invest 88:1559–1567

Chen PY, Sanders PW (1993) Role of nitric oxide synthesis in salt-sensitive hypertension in Dahl/Rapp rats. Hypertension 22:812–818

Chen PY, St John PL, Kirk KA, Abrahamson DR, Sanders PW (1993) Hypertensive nephrosclerosis in the Dahl/Rapp rat. Initial sites of injury and effect of dietary L-arginine supplementation. Lab Invest 68:174–184

Chen R, Iwai M, Wu L, Suzuki J, Min LJ, Shiuchi T, Sugaya T, Liu HW, Cui TX, Horiuchi M (2003) Important role of nitric oxide in the effect of angiotensin-converting enzyme inhibitor imidapril on vascular injury. Hypertension 42:542–547

Chenevard R, Hurlimann D, Bechir M, Enseleit F, Spieker L, Hermann M, Riesen W, Gay S, Gay RE, Neidhart M, Michel B, Lüscher TF, Noll G, Ruschitzka F (2003) Selective COX-2 inhibition improves endothelial function in coronary artery disease. Circulation 107: 405–409

Cheng ZJ, Vapaatalo H, Mervaala E (2005) Angiotensin II and vascular inflammation. Med Sci Monit 11:RA194–RA205

Cockcroft JR, Chowienczyk PJ, Benjamin N, Ritter JM (1994) Preserved endothelium-dependent vasodilatation in patients with essential hypertension. N Engl J Med 330: 1036–1040

Cockcroft JR, Chowienczyk PJ, Brett SE, Chen CP, Dupont AG, Van Nueten L, Wooding SJ, Ritter JM (1995) Nebivolol vasodilates human forearm vasculature: evidence for an L-arginine/NO-dependent mechanism. J Pharmacol Exp Ther 274:1067–1071

Cosentino F, Sill JC, Katusic ZS (1994) Role of superoxide anions in the mediation of endothelium-dependent contractions. Hypertension 23:223–235

Cosentino F, Patton S, d'Uscio LV, Werner ER, Werner-Felmayer G, Moreau P, Malinski T, Lüscher TF (1998) Tetrahydrobiopterin alters superoxide and nitric oxide release in prehypertensive rats. J Clin Invest 101:1530–1537

Creager MA, Roddy MA (1994) Effect of captopril and enalapril on endothelial function in hypertensive patients. Hypertension 24:499–505

Creager MA, Roddy MA, Coleman SM, Dzau VJ (1992) The effect of ACE inhibition on endothelium-dependent vasodilation in hypertension. J Vasc Res 29:97

d'Uscio LV, Shaw S, Barton M, Lüscher TF (1998) Losartan but not verapamil inhibits angiotensin II-induced tissue endothelin-1 increase: role of blood pressure and endothelial function. Hypertension 31:1305–1310

Dawes M, Brett SE, Chowienczyk PJ, Mant TG, Ritter JM (1999) The vasodilator action of nebivolol in forearm vasculature of subjects with essential hypertension. Br J Clin Pharmacol 48:460–463

De La Torre R, Casado A, Lopez-Fernandez E, Carrascosa D, Ramirez V, Saez J (1996) Overexpression of copper-zinc superoxide dismutase in trisomy 21. Experientia 52: 871–873

Deanfield J, Donald A, Ferri C, Giannattasio C, Halcox J, Halligan S, Lerman A, Mancia G, Oliver JJ, Pessina AC, Rizzoni D, Rossi GP, Salvetti A, Schiffrin EL, Taddei S, Webb DJ (2005) Endothelial function and dysfunction. Part I. Methodological issues for assessment in the different vascular beds: a statement by the Working Group on Endothelin and Endothelial Factors of the European Society of Hypertension. J Hypertens 23:7–17

Dechend R, Fiebler A, Lindschau C, Bischoff H, Muller D, Park JK, Dietz R, Haller H, Luft FC (2001) Modulating angiotensin II-induced inflammation by HMG Co-A reductase inhibition. Am J Hypertens 14:55S–61S

Demougeot C, Prigent-Tessier A, Marie C, Berthelot A (2005) Arginase inhibition reduces endothelial dysfunction and blood pressure rising in spontaneously hypertensive rats. J Hypertens 23:971–978

Deng AY, Rapp JP (1995) Locus for the inducible, but not a constitutive, nitric oxide synthase cosegregates with blood pressure in the Dahl salt-sensitive rat. J Clin Invest 95:2170–2177

Diederich D, Yang ZH, Bühler FR, Lüscher TF (1990) Impaired endothelium-dependent relaxations in hypertensive resistance arteries involve cyclooxygenase pathway. Am J Physiol 258:H445–H451

Dijkhorst-Oei LT, Stroes ES, Koomans HA, Rabelink TJ (1999) Acute simultaneous stimulation of nitric oxide and oxygen radicals by angiotensin II in humans in vivo. J Cardiovasc Pharmacol 33:420–424

Dohi Y, Thiel MA, Bühler FR, Lüscher TF (1990) Activation of endothelial L-arginine pathway in resistance arteries. Effect of age and hypertension. Hypertension 16:170–179

Dohi Y, Criscione L, Lüscher TF (1991) Renovascular hypertension impairs formation of endothelium-derived relaxing factors and sensitivity to endothelin-1 in resistance arteries. Br J Pharmacol 104:349–354

Dohi Y, Hahn AW, Boulanger CM, Bühler FR, Lüscher TF (1992) Endothelin stimulated by angiotensin II augments contractility of spontaneously hypertensive rat resistance arteries. Hypertension 19:131–137

Dohi Y, Criscione L, Pfeiffer K, Lüscher TF (1994) Angiotensin blockade or calcium antagonists improve endothelial dysfunction in hypertension: studies in perfused mesenteric resistance arteries. J Cardiovasc Pharmacol 24:372–379

Donckier JE, Hanet C, Berbinschi A, Galanti L, Robert A, Van Mechelen H, Pouleur H, Ketelslegers JM (1991) Cardiovascular and endocrine effects of endothelin-1 at pathophysiological and pharmacological plasma concentrations in conscious dogs. Circulation 84:2476–2484

Doucet J, Gonzalez W, Michel JB (1996) Endothelin antagonists in salt-dependent hypertension associated with renal insufficiency. J Cardiovasc Pharmacol 27:643–651

Duffy SJ, Gokce N, Holbrook M, Huang A, Frei B, Keaney JFJ, Vita JA (1999) Treatment of hypertension with ascorbic acid. Lancet 354:2048–2049

Edwards G, Dora KA, Gardener MJ, Garland CJ, Weston AH (1998) K+ is an endothelium-derived hyperpolarizing factor in rat arteries. Nature 396:269–272

Egashira K, Suzuki S, Hirooka Y, Kai H, Sugimachi M, Imaizumi T, Takeshita A (1995) Impaired endothelium-dependent vasodilation of large epicardial and resistance coronary arteries in patients with essential hypertension. Different responses to acetylcholine and substance P. Hypertension 25:201–206

Ferro CJ, Haynes WG, Hand MF, Webb DJ (2002) Forearm vasoconstriction to endothelin-1 is impaired, but constriction to sarafotoxin 6c and vasodilatation to BQ-123 unaltered, in patients with essential hypertension. Clin Sci (Lond) 103 Suppl 48:53S–58S

Fichtlscherer S, Rosenberger G, Walter G, Breuer S, Dimmeler S, Zeiher AM (2000) Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. Circulation 102:1000–1006

Fleminger G, Bousso-Mittler D, Bdolah A, Kloog Y, Sokolovsky M (1989) Immunological and structural characterization of sarafotoxin/endothelin family of peptides. Biochem Biophys Res Commun 162:1317–1323

Forte P, Copland M, Smith LM, Milne E, Sutherland J, Benjamin N (1997) Basal nitric oxide synthesis in essential hypertension. Lancet 349:837–842

Fridovich I, Freeman B (1986) Antioxidant defenses in the lung. Annu Rev Physiol 48:693–702

Frielingsdorf J, Seiler C, Kaufmann P, Vassalli G, Suter T, Hess OM (1996) Normalization of abnormal coronary vasomotion by calcium antagonists in patients with hypertension. Circulation 93:1380–1387

Fujii K, Tominaga M, Ohmori S, Kobayashi K, Koga T, Takata Y, Fumjishima M (1992) Decreased endothelium-dependent hyperpolarization to acetylcholine in smooth muscle of the mesenteric artery of spontaneously hypertensive rats. Circ Res 70:660–669

Fukui T, Ishizaka N, Rajagopalan S, Laursen JB, Capers Qt, Taylor WR, Harrison DG, de Leon H, Wilcox JN, Griendling KK (1997) p22phox mRNA expression and NADPH oxidase activity are increased in aortas from hypertensive rats. Circ Res 80:45–51

Furchgott RF, Zawadzki JV (1980) The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288:373–376

Gardiner SM, Compton AM, Kemp PA, Bennett T (1990) Regional and cardiac haemodynamic responses to glyceryl trinitrate, acetylcholine, bradykinin and endothelin-1 in conscious rats: effects of N^G-nitro-L-arginine methyl ester. Br J Pharmacol 101:632–639

Ghiadoni L, Taddei S, Virdis A, Sudano I, Di Legge V, Meola M, Di Venanzio L, Salvetti A (1998) Endothelial function and common carotid artery wall thickening in patients with essential hypertension. Hypertension 32:25–32

Ghiadoni L, Virdis A, Magagna A, Taddei S, Salvetti A (2000) Effect of the angiotensin II type 1 receptor blocker candesartan on endothelial function in patients with essential hypertension. Hypertension 35:501–506

Ghiadoni L, Magagna A, Versari D, Kardasz I, Huang Y, Taddei S, Salvetti A (2003) Different effect of antihypertensive drugs on conduit artery endothelial function. Hypertension 41:1281–1286

Goldblatt H, Lynch J, Hanzal RF, Summerville WW (1934) Studies on experimental hypertension, I: the production of persistent elevation of systolic blood pressure by means of renal ischemia. J Exp Med 59:347–379

Grunfeld S, Hamilton CA, Mesaros S, McClain SW, Dominiczak AF, Bohr DF, Malinski T (1995) Role of superoxide in the depressed nitric oxide production by the endothelium of genetically hypertensive rats. Hypertension 26:854–857

Hayakawa H, Hirata Y, Suzuki E, Sugimoto T, Matsuoka H, Kikuchi K, Nagano T, Hirobe M, Sugimoto T (1993) Mechanisms for altered endothelium-dependent vasorelaxation in isolated kidneys from experimental hypertensive rats. Am J Physiol 264:H1535–H1541

Haynes WG, Webb DJ (1994) Contribution of endogenous generation of endothelin-1 to basal vascular tone. Lancet 344:852–854

Haynes WG, Ferro CJ, O'Kane KP, Somerville D, Lomax CC, Webb DJ (1996) Systemic endothelin receptor blockade decreases peripheral vascular resistance and blood pressure in humans. Circulation 93:1860–1870

Haynes WG, Ferro CJ, Webb DJ (1998) Bosentan in essential hypertension [letter; comment]. N Engl J Med 339:346; discussion 347

Hermann M, Camici G, Fratton A, Hurlimann D, Tanner FC, Hellermann JP, Fiedler M, Thiery J, Neidhart M, Gay RE, Gay S, Lüscherr TF, Ruschitzka F (2003) Differential effects of selective cyclooxygenase-2 inhibitors on endothelial function in salt-induced hypertension. Circulation 108:2308–2311

Hermann M, Shaw S, Kiss E, Camici G, Buhler N, Chenevard R, Lüscher TF, Grone HJ, Ruschitzka F (2005) Selective COX-2 inhibitors and renal injury in salt-sensitive hypertension. Hypertension 45:193–197

Hickey KA, Rubanyi G, Paul RJ, Highsmith RF (1985) Characterization of a coronary vasoconstrictor produced by cultured endothelial cells. Am J Physiol 248:C550–C556

Hieda HS, Gomez-Sanchez CE (1990) Hypoxia increases endothelin release in bovine endothelial cells in culture, but epinephrine, norepinephrine, serotonin, histamine and angiotensin II do not. Life Sci 47:247–251

Hingorani AD, Cross J, Kharbanda RK, Mullen MJ, Bhagat K, Taylor M, Donald AE, Palacios M, Griffin GE, Deanfield JE, MacAllister RJ, Vallance P (2000) Acute systemic inflammation impairs endothelium-dependent dilatation in humans. Circulation 102:994–999

Hirata Y, Hayakawa H, Suzuki E, Kimura K, Kikuchi K, Nagano T, Hirobe M, Omata M (1995) Direct measurements of endothelium-derived nitric oxide release by stimulation of endothelin receptors in rat kidney and its alteration in salt-induced hypertension. Circulation 91:1229–1235

Hirooka Y, Imaizumi T, Masaki H, Ando S, Harada S, Momohara M, Takeshita A (1992) Captopril improves impaired endothelium-dependent vasodilation in hypertensive patients. Hypertension 20:175–180

Hishikawa K, Oemar BS, Yang Z, Lüscher TF (1997) Pulsatile stretch stimulates superoxide production and activates nuclear factor-kappa B in human coronary smooth muscle. Circ Res 81:797–803

Hocher B, Rohmeiss P, Zart R, Diekmann F, Vogt V, Metz D, Fakhury M, Gretz N, Bauer C, Koppenhagen K, et al (1995) Significance of endothelin receptor subtypes in the kidneys of spontaneously hypertensive rats: renal and hemodynamic effects of endothelin receptor antagonists. J Cardiovasc Pharmacol 26 Suppl 3:S470–S472

Hocher B, Rohmeiss P, Zart R, Diekmann F, Vogt V, Metz D, Fakhury M, Gretz N, Bauer C, Koppenhagen K, Neumayer HH, Distler A (1996) Function and expression of endothelin receptor subtypes in the kidneys of spontaneously hypertensive rats. Cardiovasc Res 31:499–510

Hocher B, George I, Rebstock J, Bauch A, Schwarz A, Neumayer HH, Bauer C (1999) Endothelin system-dependent cardiac remodeling in renovascular hypertension. Hypertension 33:816–822

Hu L, Manning RD Jr (1995) Role of nitric oxide in regulation of long-term pressure-natriuresis relationship in Dahl rats. Am J Physiol 268:H2375–H2383

Ikeda Y, Saito K, Kim JI, Yokoyama M (1995) Nitric oxide synthase isoform activities in kidney of Dahl salt-sensitive rats. Hypertension 26:1030–1034

Ikegawa R, Matsumura Y, Tsukahara Y, Takaoka M, Morimoto S (1990) Phosphoramidon, a metalloproteinase inhibitor, suppresses the secretion of endothelin-1 from cultured endothelial cells by inhibiting a big endothelin-1 converting enzyme. Biochem Biophys Res Commun 171:669–675

Inoue A, Yanagisawa M, Kimura S, Kasuya Y, Miyauchi T, Goto K, Masaki T (1989a) The human endothelin family: three structurally and pharmacologically distinct isopeptides predicted by three separate genes. Proc Natl Acad Sci U S A 86:2863–2867

Inoue A, Yanagisawa M, Takuwa Y, Mitsui Y, Kobayashi M, Masaki T (1989b) The human preproendothelin-1 gene. Complete nucleotide sequence and regulation of expression. J Biol Chem 264:14954–14959

Ito H, Hirata Y, Hiroe M, Tsujino M, Adachi S, Takamoto T, Nitta M, Taniguchi K, Marumo F (1991) ET-1 induces hypertrophy with enhanced expression of muscle specific genes in cultured neonatal rat cardiomyocytes. Circ Res 69:209–215

Jameson M, Dai FX, Lüscher T, Skopec J, Diederich A, Diederich D (1993) Endothelium-derived contracting factors in resistance arteries of young spontaneously hypertensive rats before development of overt hypertension. Hypertension 21:280–288

Joannides R, Haefeli WE, Linder L, Richard V, Bakkali EH, Thuillez C, Lüscher TF (1995a) Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. Circulation 91:1314–1319

Joannides R, Richard V, Haefeli WE, Linder L, Lüscher TF, Thuillez C (1995b) Role of basal and stimulated release of nitric oxide in the regulation of radial artery caliber in humans. Hypertension 26:327–331

Kakoki M, Hirata Y, Hayakawa H, Tojo A, Nagata D, Suzuki E, Kimura K, Goto A, Kikuchi K, Nagano T, Omata M (1999) Effects of hypertension, diabetes mellitus, and hypercholesterolemia on endothelin type B receptor-mediated nitric oxide release from rat kidney. Circulation 99:1242–1248

Kannan H, Tanaka H, Ueta Y, Hayashida Y, Kunitake T, Yamashita H (1994) Effects of centrally administered endothelin-3 on renal sympathetic nerve activity and renal blood flow in conscious rats. J Auton Nerv Syst 49:105–113

Kannel WB, Gordon T, Offutt D (1969) Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. Ann Intern Med 71: 89–105

Kanse SM, Takahashi K, Lam HC, Rees A, Warren JB, Porta M, Molinatti P, Ghatei M, Bloom SR (1991) Cytokine stimulated endothelin release from endothelial cells. Life Sci 48:1379–1384

Katusic ZS, Vanhoutte PM (1989) Superoxide anion is an endothelium-derived contracting factor. Am J Physiol 257:H33–H37

Katusic ZS, Schugel J, Cosentino F, Vanhoutte PM (1993) Endothelium-dependent contractions to oxygen-derived free radicals in the canine basilar artery. Am J Physiol 264:H859–H864

Kelm M, Feelisch M, Krebber T, Motz W, Strauer BE (1992) The role of nitric oxide in the regulation of coronary vascular resistance in arterial hypertension: comparison of normotensive and spontaneously hypertensive rats. J Cardiovasc Pharmacol 20: S183–S186

Kerr S, Brosnan MJ, McIntyre M, Reid JL, Dominiczak AF, Hamilton CA (1999) Superoxide anion production is increased in a model of genetic hypertension: role of the endothelium. Hypertension 33:1353–1358

Kiely DG, Cargill RI, Struthers AD, Lipworth BJ (1997) Cardiopulmonary effects of endothelin-1 in man. Cardiovasc Res 33:378–386

Kloog Y, Ambar I, Sokolovsky M, Kochva E, Wollberg Z, Bdolah A (1988) Sarafotoxin, a novel vasoconstrictor peptide: phosphoinositide hydrolysis in rat heart and brain. Science 242:268–270

Knuepfer MM, Han SP, Trapani AJ, Fok KF, Westfall TC (1989) Regional hemodynamic and baroreflex effects of endothelin in rats. Am J Physiol 257:H918–H926

Kohno M, Murakawa K, Yokokawa K, Yasunari K, Horio T, Kurihara N, Takeda T (1989) Production of endothelin by cultured porcine endothelial cells: modulation by adrenaline. J Hypertens Suppl 7:S130–S131

Koller A, Kaley G (1990) Prostaglandins mediate arteriolar dilation to increased blood flow velocity in skeletal muscle microcirculation. Circ Res 67:529–534

Kontos HA, Wei EP, Ellis EF, Jenkins LW, Povlishock JT, Rowe GT, Hess ML (1985) Appearance of superoxide anion radical in cerebral extracellular space during increased prostaglandin synthesis in cats. Circ Res 57:142–151

Kourembanas S, Marsden PA, McQuillan LP, Faller DV (1991) Hypoxia induces endothelin gene expression and secretion in cultured human endothelium. J Clin Invest 88:1054–1057

Küng CF, Lüscher TF (1995) Different mechanisms of endothelial dysfunction with aging and hypertension in rat aorta. Hypertension 25:194–200

Lariviere R, Day R, Schiffrin EL (1993a) Increased expression of endothelin-1 gene in blood vessels of deoxycorticosterone acetate-salt hypertensive rats. Hypertension 21:916–920

Lariviere R, Thibault G, Schiffrin EL (1993b) Increased endothelin-1 content in blood vessels of deoxycorticosterone acetate-salt hypertensive but not in spontaneously hypertensive rats. Hypertension 21:294–300

Lariviere R, Sventek P, Schiffrin EL (1995) Expression of endothelin-1 gene in blood vessels of adult spontaneously hypertensive rats. Life Sci 56:1889–1896

Laursen JB, Rajagopalan S, Galis Z, Tarpey M, Freeman BA, Harrison DG (1997) Role of superoxide in angiotensin II-induced but not catecholamine-induced hypertension. Circulation 95:588–593

Lee J, Choi KC, Yeum CH, Kim W, Yoo K, Park JW, Yoon PJ (1995) Impairment of endothelium-dependent vasorelaxation in chronic two-kidney, one clip hypertensive rats. Nephrol Dial Transplant 10:619–623

Lepori M, Sartori C, Trueb L, Owlya R, Nicod P, Scherrer U (1998) Haemodynamic and sympathetic effects of inhibition of nitric oxide synthase by systemic infusion of N(G)-monomethyl-L-arginine into humans are dose dependent. J Hypertens 16:519–523

Levanon D, Lieman-Hurwitz J, Dafni N, Wigderson M, Sherman L, Bernstein Y, Laver-Rudich Z, Danciger E, Stein O, Groner Y (1985) Architecture and anatomy of the chromosomal locus in human chromosome 21 encoding the Cu/Zn superoxide dismutase. EMBO J 4:77–84

Lewis SJ, Ohta H, Machado B, Bates JN, Talman WT (1991) Microinjection of S-nitrosocysteine into the nucleus tractus solitarii decreases arterial pressure and heart rate via activation of soluble guanylate cyclase. Eur J Pharmacol 202:135–136

Li JS, Lariviere R, Schiffrin EL (1994) Effect of a nonselective endothelin antagonist on vascular remodeling in deoxycorticosterone acetate-salt hypertensive rats. Evidence for a role of endothelin in vascular hypertrophy. Hypertension 24:183–188

Li L, Fink GD, Watts SW, Northcott CA, Galligan JJ, Pagano PJ, Chen AF (2003) Endothelin-1 increases vascular superoxide via endothelin(A)-NADPH oxidase pathway in low-renin hypertension. Circulation 107:1053–1058

Linder L, Kiowski W, Bühler FR, Lüscher TF (1990) Indirect evidence for release of endothelium-derived relaxing factor in human forearm circulation in vivo. Blunted response in essential hypertension. Circulation 81:1762–1767

Lüscher TF (1990) Imbalance of endothelium-derived relaxing and contracting factors. A new concept in hypertension? Am J Hypertens 317:317–330

Lüscher TF, Noll G (1997) Endothelium-derived vasoactive substances. In: Braunwald E (ed) Heart disease, 5 edn. WB Saunders, Philadelphia, pp 1165

Lüscher TF, Vanhoutte PM (1986) Endothelium-dependent contractions to acetylcholine in the aorta of the spontaneously hypertensive rat. Hypertension 8:344–348

Lüscher TF, Vanhoutte PM (1990) The endothelium: modulator of cardiovascular function. CRC Press, Boca Ranton

Lüscher TF, Romero JC, Vanhoutte PM (1986) Bioassay of endothelium-derived substances in the aorta of normotensive and spontaneously hypertensive rats. J Hypertens 4 Suppl 6:81

Lüscher TF, Raij L, Vanhoutte PM (1987a) Endothelium-dependent vascular responses in normotensive and hypertensive Dahl rats. Hypertension 9:157–163

Lüscher TF, Vanhoutte PM, Raij L (1987b) Antihypertensive treatment normalizes decreased endothelium-dependent relaxations in rats with salt-induced hypertension. Hypertension 9 Suppl 3:193–197

Lüscher TF, Yang Z, Tschudi M, Von SL, Stulz P, Boulanger C, Siebenmann R, Turina M, Bühler FR (1990) Interaction between endothelin-1 and endothelium-derived relaxing factor in human arteries and veins. Circ Res 66:1088–1094

Lyons D, Webster J, Benjamin N (1994) The effect of antihypertensive therapy on responsiveness to local intra-arterial NG-monomethyl-L-arginine in patients with essential hypertension. J Hypertens 12:1047–1052

Lysko PG, Feuerstein G, Pullen M, Wu HL, Nambi P (1991) Identification of endothelin receptors in cultured cerebellar neurons. Neuropeptides 18:83–86

Machha A, Mustafa MR (2005) Chronic treatment with flavonoids prevents endothelial dysfunction in spontaneously hypertensive rat aorta. J Cardiovasc Pharmacol 46:36–40

Maeso R, Rodrigo E, Munoz-Garcia R, Navarro-Cid J, Ruilope LM, Cachofeiro V, Lahera V (1998) Chronic treatment with losartan ameliorates vascular dysfunction induced by aging in spontaneously hypertensive rats. J Hypertens 16:665–672

Matsuoka H, Itoh S, Kimoto M, Kohno K, Tamai O, Wada Y, Yasukawa H, Iwami G, Okuda S, Imaizumi T (1997) Asymmetrical dimethylarginine, an endogenous nitric oxide synthase inhibitor, in experimental hypertension. Hypertension 29:242–247

McAllister AS, Atkinson AB, Johnston GD, Hadden DR, Bell PM, McCance DR (1999) Basal nitric oxide production is impaired in offspring of patients with essential hypertension. Clin Sci (Lond) 97:141–147

McIntyre M, Hamilton CA, Rees DD, Reid JL, Dominiczak AF (1997) Sex differences in the abundance of endothelial nitric oxide in a model of genetic hypertension. Hypertension 30:1517–1524

Millgard J, Lind L (1998) Acute hypertension impairs endothelium-dependent vasodilation. Clin Sci (Lond) 94:601–607

Millgard J, Hagg A, Sarabi M, Lind L (1998) Captopril, but not nifedipine, improves endothelium-dependent vasodilation in hypertensive patients. J Hum Hypertens 12: 511–516

Miyamori I, Takeda Y, Yoneda T, Iki K, Takeda R (1991) Interleukin-2 enhances the release of endothelin-1 from the rat mesenteric artery. Life Sci 49:1295–1300

Miyauchi T, Ishikawa T, Tomobe Y, Yanagisawa M, Kimura S, Sugishita Y, Ito I, Goto K, Masaki T (1989) Characteristics of pressor response to endothelin in spontaneously hypertensive and Wistar-Kyoto rats. Hypertension 14:427–434

Miyauchi T, Yanagisawa M, Iida K, Ajisaka R, Suzuki N, Fujino M, Goto K, Masaki T, Sugishita Y (1992) Age- and sex-related variation of plasma endothelin-1 concentration in normal and hypertensive subjects. Am Heart J 123:1092–1093

Moncada S, Gryglewski R, Bunting S, Vane JR (1976) An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. Nature 263:663–665

Moreau P, d'Uscio LV, Shaw S, Takase H, Barton M, Lüscher TF (1997) Angiotensin II increases tissue endothelin and induces vascular hypertrophy: reversal by ET(A)-receptor antagonist. Circulation 96:1593–1597

Morrison RA, McGrath A, Davidson G, Brown JJ, Murray GD, Lever AF (1996) Low blood pressure in Down's syndrome, a link with Alzheimer's disease? Hypertension 28:569–575

Mosqueda-Garcia R, Appalsamy M, Fernandez-Violante R, Hamakubo T (1998) Modulatory effects of endothelin on baroreflex activation in the nucleus of the solitary tract. Eur J Pharmacol 351:203–207

Nakamoto H, Suzuki H, Murakami M, Kageyama Y, Naitoh M, Sakamaki Y, Ohishi A, Saruta T (1991) Different effects of low and high doses of endothelin on haemodynamics and hormones in the normotensive conscious dog. J Hypertens 9:337–344

Nakazono K, Watanabe N, Matsuno K, Sasaki J, Sato T, Inoue M (1991) Does superoxide underlie the pathogenesis of hypertension? Proc Natl Acad Sci U S A 88:10045–10048

Nambi P, Pullen M, Feuerstein G (1990) Identification of endothelin receptors in various regions of rat brain. Neuropeptides 16:195–199

Nava E, Noll G, Lüscher TF (1995) Increased activity of constitutive nitric oxide synthase in cardiac endothelium in spontaneous hypertension. Circulation 91:2310–2313

Nava E, Farre AL, Moreno C, Casado S, Moreau P, Cosentino F, Lüscher TF (1998) Alterations to the nitric oxide pathway in the spontaneously hypertensive rat. J Hypertens 16:609–615

Ni Z, Oveisi F, Vaziri ND (1999) Nitric oxide synthase isotype expression in salt-sensitive and salt-resistant Dahl rats. Hypertension 34:552–557

Nicaud V, Poirier O, Behague I, Herrmann SM, Mallet C, Troesch A, Bouyer J, Evans A, Luc G, Ruidavets JB, Arveiler D, Bingham A, Tiret L, Cambien F (1999) Polymorphisms of the endothelin-A and -B receptor genes in relation to blood pressure and myocardial infarction: the Etude Cas-Temoins sur l'Infarctus du Myocarde (ECTIM) Study. Am J Hypertens 12:304–310

Nohria A, Garrett L, Johnson W, Kinlay S, Ganz P, Creager MA (2003) Endothelin-1 and vascular tone in subjects with atherogenic risk factors. Hypertension 42:43–48

Noll G, Lang MG, Tschudi MR, Ganten D, Lüscher TF (1997) Endothelial vasoconstrictor prostanoids modulate contractions to acetylcholine and ANG II in Ren-2 rats. Am J Physiol 272:H493–H500

O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr (1999) Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 340:14–22

Ohnaka K, Takayanagi R, Nishikawa M, Haji M, Nawata H (1993) Purification and characterization of a phosphoramidon-sensitive endothelin-converting enzyme in porcine aortic endothelium. J Biol Chem 268:26759–26766

Ohta K, Hirata Y, Imai T, Kanno K, Emori T, Shichiri M, Marumo F (1990) Cytokine-induced release of endothelin-1 from porcine renal epithelial cell line. Biochem Biophys Res Commun 169:578–584

Okahara K, Sun B, Kambayashi J (1998) Upregulation of prostacyclin synthesis-related gene expression by shear stress in vascular endothelial cells. Arterioscler Thromb Vasc Biol 18:1922–1926

Palmer RM, Ferrige AG, Moncada S (1987) Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 327:524–526

Palmer RM, Ashton DS, Moncada S (1988a) Vascular endothelial cells synthesize nitric oxide from L-arginine. Nature 333:664–666

Palmer RMJ, Rees DD, Ashton DS, Moncada S (1988b) L-Arginine is the physiological precursor for the formation of nitric oxide in endothelium-dependent relaxation. Biochem Biophys Res Commun 153:1251–1256

Palmer RM, Bridge L, Foxwell NA, Moncada S (1992) The role of nitric oxide in endothelial cell damage and its inhibition by glucocorticoids. Br J Pharmacol 105:11–12

Panza JA, Quyyumi AA, Brush JJ, Epstein SE (1990) Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med 323:22–27

Panza JA, Casino PR, Badar DM, Quyyumi AA (1993a) Effect of increased availability of endothelium-derived nitric oxide precursor on endothelium-dependent vascular relaxation in normal subjects and in patients with essential hypertension. Circulation 87:1475–1481

Panza JA, Casino PR, Kilcoyne CM, Quyyumi AA (1993b) Role of endothelium-derived nitric oxide in the abnormal endothelium-dependent vascular relaxation of patients with essential hypertension. Circulation 87:1468–1474

Panza JA, Quyyumi AA, Callahan TS, Epstein SE (1993c) Effect of antihypertensive treatment on endothelium-dependent vascular relaxation in patients with essential hypertension. J Am Coll Cardiol 21:1145–1151

Panza JA, Casino PR, Kilcoyne CM, Quyyumi AA (1994) Impaired endothelium-dependent vasodilation in patients with essential hypertension: evidence that the abnormality is not at the muscarinic receptor level. J Am Coll Cardiol 23:1610–1616

Panza JA, Garcia CE, Kilcoyne CM, Quyyumi AA, Cannon RO 3rd (1995) Impaired endothelium-dependent vasodilation in patients with essential hypertension. Evidence that nitric oxide abnormality is not localized to a single signal transduction pathway. Circulation 91:1732–1738

Perticone F, Ceravolo R, Maio R, Ventura G, Zingone A, Perrotti N, Mattioli PL (1998) Angiotensin-converting enzyme gene polymorphism is associated with endothelium-dependent vasodilation in never treated hypertensive patients. Hypertension 31:900–905

Perticone F, Maio R, Ceravolo R, Cosco C, Cloro C, Mattioli PL (1999a) Relationship between left ventricular mass and endothelium-dependent vasodilation in never-treated hypertensive patients. Circulation 99:1991–1996

Perticone F, Ceravolo R, Maio R, Ventura G, Iacopino S, Cuda G, Mastroroberto P, Chello M, Mattioli PL (1999b) Calcium antagonist isradipine improves abnormal endothelium-dependent vasodilation in never treated hypertensive patients. Cardiovasc Res 41:299–306

Pohl U, Holtz J, Busse R, Bassenge E (1986) Crucial role of endothelium in the vasodilator response to increased flow in vivo. Hypertension 8:37–44

Radomski MW, Palmer RM, Moncada S (1987) Comparative pharmacology of endothelium-derived relaxing factor, nitric oxide and prostacyclin in platelets. Br J Pharmacol 92:181–187

Rajagopalan S, Kurz S, Munzel T, Tarpey M, Freeman BA, Griendling KK, Harrison DG (1996) Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J Clin Invest 97:1916–1923

Richard V, Tanner FC, Tschudi M, Lüscher TF (1990) Different activation of L-arginine pathway by bradykinin, serotonin, and clonidine in coronary arteries. Am J Physiol 259:H1433–H1439

Rodrigo E, Maeso R, Munoz-Garcia R, Navarro-Cid J, Ruilope LM, Cachofeiro V, Lahera V (1997) Endothelial dysfunction in spontaneously hypertensive rats: consequences of chronic treatment with losartan or captopril. J Hypertens 15:613–618

Ross R (1999) Atherosclerosis—an inflammatory disease. N Engl J Med 340:115–126

Rossi GP, Albertin G, Franchin E, Sacchetto A, Cesari M, Palu G, Pessina AC (1995) Expression of the endothelin-converting enzyme gene in human tissues. Biochem Biophys Res Commun 211:249–253

Rossi GP, Colonna S, Pavan E, Albertin G, Della Rocca F, Gerosa G, Casarotto D, Sartore S, Pauletto P, Pessina AC (1999) Endothelin-1 and its mRNA in the wall layers of human arteries ex vivo. Circulation 99:1147–1155

Rossi GP, Ganzaroli C, Cesari M, Maresca A, Plebani M, Nussdorfer GG, Pessina AC (2003) Endothelin receptor blockade lowers plasma aldosterone levels via different mechanisms in primary aldosteronism and high-to-normal renin hypertension. Cardiovasc Res 57:277–283

Rubanyi GM, Vanhoutte PM (1986) Superoxide anions and hyperoxia inactivate endothelium-derived relaxing factor. Am J Physiol 250:H822–H827

Rubanyi GM, Romero JC, Vanhoutte PM (1986) Flow-induced release of endothelium-derived relaxing factor. Am J Physiol 250:H1145–H1149

Rudd MA, Trolliet M, Hope S, Scribner AW, Daumerie G, Toolan G, Cloutier T, Loscalzo J (1999) Salt-induced hypertension in Dahl salt-resistant and salt-sensitive rats with NOS II inhibition. Am J Physiol 277:H732–H739

Saito Y, Nakao K, Mukoyama M, Imura H (1990) Increased plasma endothelin level in patients with essential hypertension [letter]. N Engl J Med 322:205

Sartori C, Lepori M, Scherrer U (2005) Interaction between nitric oxide and the cholinergic and sympathetic nervous system in cardiovascular control in humans. Pharmacol Ther 106:209–220

Schiffrin EL (2005) Vascular endothelin in hypertension. Vascul Pharmacol 43:19–29

Schiffrin EL, Deng LY (1996) Structure and function of resistance arteries of hypertensive patients treated with a beta-blocker or a calcium channel antagonist. J Hypertens 14:1247–1255

Schiffrin EL, Lariviere R, Li JS, Sventek P, Touyz RM (1995a) Deoxycorticosterone acetate plus salt induces overexpression of vascular endothelin-1 and severe vascular hypertrophy in spontaneously hypertensive rats. Hypertension 25:769–773

Schiffrin EL, Deng LY, Larochelle P (1995b) Progressive improvement in the structure of resistance arteries of hypertensive patients after 2 years of treatment with an angiotensin I-converting enzyme inhibitor. Comparison with effects of a beta-blocker. Am J Hypertens 8:229–236

Scotland RS, Madhani M, Chauhan S, Moncada S, Andresen J, Nilsson H, Hobbs AJ, Ahluwalia A (2005) Investigation of vascular responses in endothelial nitric oxide synthase/cyclooxygenase-1 double-knockout mice: key role for endothelium-derived hyperpolarizing factor in the regulation of blood pressure in vivo. Circulation 111: 796–803

Sekiguchi F, Yanamoto A, Sunano S (2004) Superoxide dismutase reduces the impairment of endothelium-dependent relaxation in the spontaneously hypertensive rat aorta. J Smooth Muscle Res 40:65–74

Sharma P, Hingorani A, Jia H, Hopper R, Brown MJ (1999) Quantitative association between a newly identified molecular variant in the endothelin-2 gene and human essential hypertension. J Hypertens 17:1281–1287

Shimada K, Takahashi M, Tanzawa K (1994) Cloning and functional expression of endothelin-converting enzyme from rat endothelial cells. J Biol Chem 269:18275–18278

Shimokawa H, Yasutake H, Fujii K, Owada MK, Nakaike R, Fukumoto Y, Takayanagi T, Nagao T, Egashira K, Fujishima M, Takeshita A (1996) The importance of the hyperpolarizing mechanism increases as the vessel size decreases in endothelium-dependent relaxations in rat mesenteric circulation. J Cardiovasc Pharmacol 28:703–711

Shirakami G, Nakao K, Saito Y, Magaribuchi T, Jougasaki M, Mukoyama M, Arai H, Hosoda K, Suga S, Ogawa Y, et al (1991) Acute pulmonary alveolar hypoxia increases lung and plasma endothelin-1 levels in conscious rats. Life Sci 48:969–976

Simchon S, Manger W, Blumberg G, Brensilver J, Cortell S (1996) Impaired renal vasodilation and urinary cGMP excretion in Dahl salt-sensitive rats. Hypertension 27:653–657

Sorensen SS (1991) Radio-immunoassay of endothelin in human plasma. Scand J Clin Lab Invest 51:615–623

Sorensen SS, Madsen JK, Pedersen EB (1994) Systemic and renal effect of intravenous infusion of endothelin-1 in healthy human volunteers. Am J Physiol 266:F411–F418

Spieker LE, Corti R, Binggeli C, Lüscher TF, Noll G (2000a) Baroreceptor dysfunction induced by nitric oxide synthase inhibition in humans. J Am Coll Cardiol 36:213–218

Spieker LE, Noll G, Ruschitzka FT, Maier W, Lüscher TF (2000b) Working under pressure: the vascular endothelium in arterial hypertension. J Hum Hypertens 14:617–630

Spieker LE, Noll G, Ruschitzka FT, Lüscher TF (2001) Endothelin receptor antagonists in congestive heart failure: a new therapeutic principle for the future? J Am Coll Cardiol 37:1493–1505

Stamler JS, Singel DJ, Loscalzo J (1992) Biochemistry of nitric oxide and its redox-activated forms. Science 258:1898–1902

Stamler JS, Loh E, Roddy MA, Currie KE, Creager MA (1994) Nitric oxide regulates basal systemic and pulmonary vascular resistance in healthy humans. Circulation 89: 2035–2040

Stevens PA, Brown MJ (1995) Genetic variability of the ET-1 and the ETA receptor genes in essential hypertension. J Cardiovasc Pharmacol 26 Suppl 3:S9–S12

Stroes E, Hijmering M, van Zandvoort M, Wever R, Rabelink TJ, van Faassen EE (1998) Origin of superoxide production by endothelial nitric oxide synthase. FEBS Lett 438:161–164

Sudano I, Taddei S, Virdis A, Ghiadoni L, Haq BA, Noll G, Lüscher TF, Salvetti A (1998) Nifedipine enhances endothelium-dependent relaxation and inhibits contractions to endothelin-1 and phenylephrine in hypertension [abstract]. J Hypertens 16:1115

Taddei S, Virdis A, Mattei P, Arzilli F, Salvetti A (1992) Endothelium-dependent forearm vasodilation is reduced in normotensive subjects with familial history of hypertension. J Cardiovasc Pharmacol 20:S193–S195

Taddei S, Mattei P, Virdis A, Sudano I, Ghiadoni L, Salvetti A (1994) Effect of potassium on vasodilation to acetylcholine in essential hypertension. Hypertension 23:485–490

Taddei S, Virdis A, Mattei P, Ghiadoni L, Gennari A, Fasolo CB, Sudano I, Salvetti A (1995) Aging and endothelial function in normotensive subjects and patients with essential hypertension. Circulation 91:1981–1987

Taddei S, Virdis A, Mattei P, Ghiadoni L, Fasolo CB, Sudano I, Salvetti A (1997a) Hypertension causes premature aging of endothelial function in humans. Hypertension 29:736–743

Taddei S, Virdis A, Ghiadoni L, Magagna A, Salvetti A (1997b) Cyclooxygenase inhibition restores nitric oxide activity in essential hypertension. Hypertension 29:274–279

Taddei S, Virdis A, Ghiadoni L, Uleri S, Magagna A, Salvetti A (1997c) Lacidipine restores endothelium-dependent vasodilation in essential hypertensive patients. Hypertension 30:1606–1612

Taddei S, Virdis A, Ghiadoni L, Mattei P, Salvetti A (1998a) Effects of angiotensin converting enzyme inhibition on endothelium-dependent vasodilatation in essential hypertensive patients. J Hypertens 16:447–456

Taddei S, Virdis A, Ghiadoni L, Magagna A, Salvetti A (1998b) Vitamin C improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential hypertension. Circulation 97:2222–2229

Taddei S, Virdis A, Ghiadoni L, Sudano I, Notari M, Salvetti A (1999a) Vasoconstriction to endogenous endothelin-1 is increased in the peripheral circulation of patients with essential hypertension. Circulation 100:1680–1683

Taddei S, Ghiadoni L, Virdis A, Buralli S, Salvetti A (1999b) Vasodilation to bradykinin is mediated by an ouabain-sensitive pathway as a compensatory mechanism for impaired nitric oxide availability in essential hypertensive patients. Circulation 100:1400–1405

Takahashi M, Matsushita Y, Iijima Y, Tanzawa K (1993) Purification and characterization of endothelin-converting enzyme from rat lung. J Biol Chem 268:21394–21398

Takase B, Uehata A, Akima T, Nagai T, Nishioka T, Hamabe A, Satomura K, Ohsuzu F, Kurita A (1998) Endothelium-dependent flow-mediated vasodilation in coronary and brachial arteries in suspected coronary artery disease. Am J Cardiol 82:1535–9, A7–A8

Takase H, Moreau P, Kung CF, Nava E, Lüscher TF (1996) Antihypertensive therapy prevents endothelial dysfunction in chronic nitric oxide deficiency. Effect of verapamil and trandolapril. Hypertension 27:25–31

Tan DY, Meng S, Manning RD Jr (1999) Role of neuronal nitric oxide synthase in Dahl salt-sensitive hypertension. Hypertension 33:456–461

Taylor SG, Weston AH (1988) Endothelium-derived hyperpolarizing factor: a new endogenous inhibitor from the vascular endothelium. Trends Pharmacol Sci 9:272–274

Thomson L, Trujillo M, Telleri R, Radi R (1995) Kinetics of cytochrome c2+ oxidation by peroxynitrite: implications for superoxide measurements in nitric oxide-producing biological systems. Arch Biochem Biophys 319:491–497

Title LM, Giddens K, McInerney MM, McQueen MJ, Nassar BA (2003) Effect of cyclooxygenase-2 inhibition with rofecoxib on endothelial dysfunction and inflammatory markers in patients with coronary artery disease. J Am Coll Cardiol 42:1747–1753

Treasure CB, Klein JL, Vita JA, Manoukian SV, Renwick GH, Selwyn AP, Ganz P, Alexander RW (1993) Hypertension and left ventricular hypertrophy are associated with impaired endothelium-mediated relaxation in human coronary resistance vessels. Circulation 87:86–93

Tschudi MR, Criscione L, Novosel D, Pfeiffer K, Lüscher TF (1994) Antihypertensive therapy augments endothelium-dependent relaxations in coronary arteries of spontaneously hypertensive rats. Circulation 89:2212–2218

Tschudi MR, Mesaros S, Lüscher TF, Malinski T (1996) Direct in situ measurement of nitric oxide in mesenteric resistance arteries. Increased decomposition by superoxide in hypertension. Hypertension 27:32–35

Turrens JF, Boveris A (1980) Generation of superoxide anion by the NADH dehydrogenase of bovine heart mitochondria. Biochem J 191:421–427

Vallance P, Collier J, Moncada S (1989) Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. Lancet 2:997–1000

Van de Voorde J, Vanheel B, Leusen I (1992) Endothelium-dependent relaxation and hyperpolarization in aorta from control and renal hypertensive rats. Circ Res 70:1–8

van den Buuse M, Itoh S (1993) Central effects of endothelin on baroreflex of spontaneously hypertensive rats. J Hypertens 11:379–387

Van Nueten L, De Cree J (1998) Nebivolol: comparison of the effects of dl-nebivolol, d-nebivolol, l-nebivolol, atenolol, and placebo on exercise-induced increases in heart rate and systolic blood pressure. Cardiovasc Drugs Ther 12:339–344

Vandermeersch S, Stefanovic V, Hus-Citharel A, Ardaillou R, Dussaule JC, Chansel D (2003) AT1 receptor expression in glomeruli from NO-deficient rats. Nephron Exp Nephrol 95:e119–e128

Vanhoutte PM (1987) Vascular physiology: the end of the quest? [news]. Nature 327:459–460

Verma S, Raj SR, Shewchuk L, Mather KJ, Anderson TJ (2001) Cyclooxygenase-2 blockade does not impair endothelial vasodilator function in healthy volunteers: randomized evaluation of rofecoxib versus naproxen on endothelium-dependent vasodilatation. Circulation 104:2879–2882

Vierhapper H, Wagner O, Nowotny P, Waldhausl W (1990) Effect of endothelin-1 in man. Circulation 81:1415–1418

Wagner OF, Christ G, Wojta J, Vierhapper H, Parzer S, Nowotny PJ, Schneider B, Waldhausl W, Binder BR (1992) Polar secretion of endothelin-1 by cultured endothelial cells. J Biol Chem 267:16066–16068

Wallin BG, Sundlof G, Stromgren E, Aberg H (1984) Sympathetic outflow to muscles during treatment of hypertension with metoprolol. Hypertension 6:557–562

Widlansky ME, Price DT, Gokce N, Eberhardt RT, Duffy SJ, Holbrook M, Maxwell C, Palmisano J, Keaney JF Jr, Morrow JD, Vita JA (2003) Short- and long-term COX-2 inhibition reverses endothelial dysfunction in patients with hypertension. Hypertension 42:310–315

Witte DR, Westerink J, de Koning EJ, van der Graaf Y, Grobbee DE, Bots ML (2005) Is the association between flow-mediated dilation and cardiovascular risk limited to low-risk populations? J Am Coll Cardiol 45:1987–1993

Woods M, Bishop-Bailey D, Pepper JR, Evans TW, Mitchell JA, Warner TD (1998) Cytokine and lipopolysaccharide stimulation of endothelin-1 release from human internal mammary artery and saphenous vein smooth-muscle cells. J Cardiovasc Pharmacol 31 Suppl 1:S348–S350

Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yazaki Y, Goto K, Masaki T (1988) A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 332:411–415

Yang Z, Bauer E, von Segesser L, Stulz P, Turina M, Lüscher TF (1990a) Different mobilization of calcium in endothelin-1-induced contractions in human arteries and veins: effects of calcium antagonists. J Cardiovasc Pharmacol 16:654–660

Yang ZH, Richard V, von Segesser L, Bauer E, Stulz P, Turina M, Lüscher TF (1990b) Threshold concentrations of endothelin-1 potentiate contractions to norepinephrine and serotonin in human arteries. A new mechanism of vasospasm? Circulation 82:188–195

Yang ZH, von Segesser L, Bauer E, Stulz P, Turina M, Lüscher TF (1991) Different activation of the endothelial L-arginine and cyclooxygenase pathway in the human internal mammary artery and saphenous vein. Circ Res 68:52–60

Yang Z, Krasnici N, Lüscher TF (1999) Endothelin-1 potentiates smooth muscle cell growth to PDGF: role of ETA and ETB receptor blockade. Circulation 100:5–8

Yavuz D, Koc M, Toprak A, Akpinar I, Velioglu A, Deyneli O, Haklar G, Akalin S (2003) Effects of ACE inhibition and AT1-receptor antagonism on endothelial function and insulin sensitivity in essential hypertensive patients. J Renin Angiotensin Aldosterone Syst 4:197–203

Yoshizumi M, Kurihara H, Sugiyama T, Takaku F, Yanagisawa M, Masaki T, Yazaki Y (1989) Hemodynamic shear stress stimulates endothelin production by cultured endothelial cells. Biochem Biophys Res Commun 161:859–864

Zafari AM, Ushio-Fukai M, Akers M, Yin Q, Shah A, Harrison DG, Taylor WR, Griendling KK (1998) Role of NADH/NADPH oxidase-derived H2O2 in angiotensin II-induced vascular hypertrophy. Hypertension 32:488–495