

11th International Symposium on Mechanisms of Vasodilation

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Changes in diameter of large arteries and veins, together with the peripheral resistance offered by the small arteries/arterioles of the microcirculation, are essential for the regulation of the function of the cardiovascular system. If disturbed, this results in major implications for diseases of the heart, brain, kidney, or the lower limbs [1].

In response to this, Paul M. Vanhoutte, MD, PhD, initiated a series of international symposia on the mechanisms of vasodilatation in Antwerp in 1977. In the following decades, he continued to organise a symposium every three to four years (fig. 1). In 1986, the 4th International Symposium on Vasodilatation had a historic impact on the way we think about cardiovascular control, because Robert R. Furchgott proposed in his presentation, with a few handwritten transparencies, that EDRF, the long sought-for endothelium-derived relaxing factor released by acetylcholine in numerous blood vessels, was in fact nitric oxide [2]. In the same session, Louis Ignarro presented his studies on nitric oxide and demonstrated that this free radical is a potent vasodilator in arteries and veins [3]. Salvador Moncada attended that meeting and returned home to Beckenham near London where he performed crucial experiments and demonstrated that the hypothesis was true. The results of his work were published in *Nature* in 1987 [4], accompanied by an editorial authored by the director of the symposium, Paul M. Vanhoutte, wherein he asked the question whether or not nitric oxide is the only answer [5]. Later, the enzymes responsible for the formation of nitric oxide, the family of nitric oxide synthases, were discovered [6].

The symposium has become highly regarded as the international community became increasingly engaged in vascular biology and those interested in endothelium-dependent responses [7] sought symposia for exchange and discussion. It was, therefore, an honour for the University of Zurich to be able to host the symposium this October, with the participation of over 100 scientists from the USA, Canada, Europe, Japan, China and Australia (fig. 2). It has become a tradition to invite the most prominent cardiovascular scientists to give a series of named lectures.

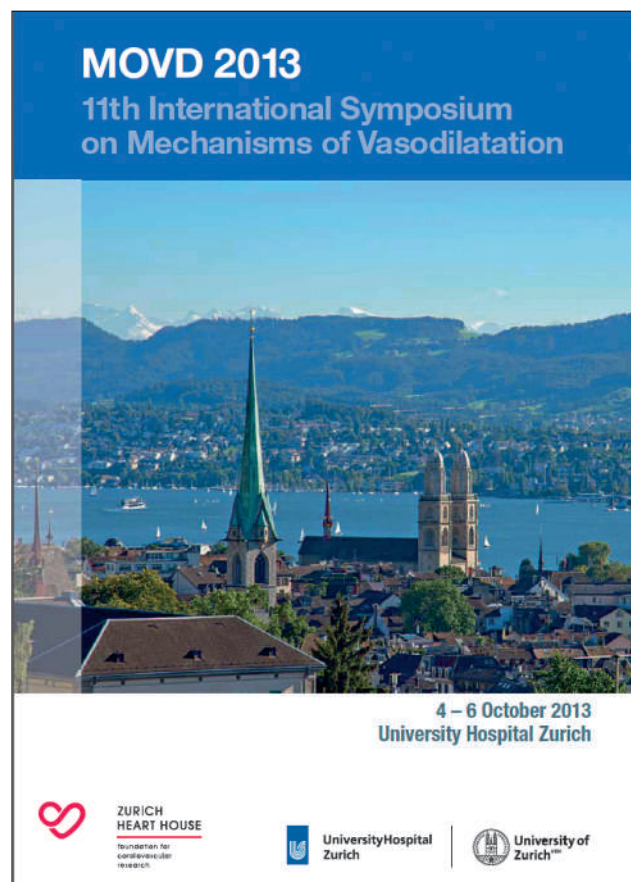


Figure 1

The 11th International Symposium on Mechanisms of Vasodilation 2013.

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Figure 2

Participants of the 11th International Symposium on Mechanisms of Vasodilatation 2013 in Zurich from Australia, Europe, USA, Canada, Japan and China.

The sympathetic system in hypertension and heart failure

Professor Murray Esler from Melbourne, Australia, gave the *John T. Shepherd Lecture*. Dr Shepherd was an eminent human physiologist who introduced world-class vascular research into the Mayo Clinic and contributed immensely to our understanding of the reflex control of the circulation. Murray Esler is Director of the Baker IDI Heart and Diabetes Institute in Melbourne and physician at the Albert Hospital, where he is Associate Director of the Heart Centre (fig. 3). He has contributed enormously to understanding of the neuronal control of the circulation, using microneurography and norepinephrine spillover in humans *in vivo* [8]. Prof. Esler was able to show that the sympathetic nervous system is also a crucial regulator of the circulation in humans and, in particular, contributes to diseases such as hypertension and heart failure. In particular, his experiments in the area of renal circulation have led to the development of renal nerve ablation as a novel and promising strategy to treat patients with resistant hypertension [9, 10].

In the same session, Uta Hoppe, Director of the Department of Internal Medicine II, Cardiology and Intensive Care Medicine at the Paracelsus Medical University Salzburg, Austria, reported on novel technologies for performing renal nerve ablation, from the simple single electrode system to multielectrode baskets [11], multielectrode wires and balloons using radiofrequency energy, neurotoxins or ultrasound. In the same session, Christian Templin from Zurich demonstrated that renal lesions are induced with the available technologies: endothelial oedema, endothelial

detachment, thrombus formation and diffuse vaso-spasm [12]. On the basis of these results, pretreatment of patients with aspirin and/or adenosine diphosphate receptor antagonists has been recommended, to avoid thrombus formation during the procedure. Felix Mah-



Figure 3

The John T. Shepherd lecturer 2013, Murray Esler, MD PhD, from Melbourne, with the chairman of the session Richard Cohen, MD PhD, from Boston. With this lecture the work of the late John T. Shepherd, who was an eminent integrative physiologist who contributed to our understanding of neurogenic cardiovascular control at the Mayo Clinic, is remembered.

foud of the Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, in Homburg, Germany, finally reviewed the clinical effectiveness of renal nerve ablation, which in patients with severe or treatment-resistant hypertension is already convincing on the basis of the available data, with a blood pressure decrease of around 30/10 mm Hg after 3 to 12 months [8, 13, 14].

Endothelium-dependent relaxations

After original research presentations from Europ, Japan and the USA, the 7th *Robert F. Furchgott Lecture*, in honour of the discoverer of endothelium-dependent relaxations and nitric oxide, for which he was awarded the Nobel Price in Medicine and Physiology in 1998, was scheduled. This year's awardee was Dr Yu Chuang from China, who was introduced by William B. Campbell. His lecture, titled "PPAR agonists preserve endothelial function by taking different routes", described how these therapeutic agents affect the intricate relationships between adipokines, cyclooxygenase(s) and reactive oxygen species in the genesis of endothelial dysfunction, leading to abnormal production of endothelium-derived vasoconstrictor prostanoids coupled to reduced release of nitric oxide.

Novel vasoactive peptides

Novel vasoactive peptides are of high interest currently, particularly in patients with heart failure. For that reason, a symposium on vasodilator and natriuretic peptides, with a particular focus on heart failure, was held. Mario Bigazzi, an internist from Prosperius University in Florence, Italy, who was one of the first cardiovascular scientists to study relaxin, gave an impressive overview of the importance of this peptide for the adaptation of the circulation in pregnancy [15]. The physiological properties of relaxin obviously lend themselves to therapeutic applications, which eventually led to the development of serelaxin, a synthetic analogue of the naturally occurring peptide, as a novel treatment for acute heart failure. Marco Metra, Professor of Cardiology at the University of Brescia, Italy, reviewed the current evidence for its use in heart failure, with an impressive reduction in mortality in patients presenting in the emergency department with acute dyspnoea and other signs of acute cardiac decompensation [16, 17, 18]. Lastly, Stefan Anker from the Charité in Berlin, Germany, discussed a new peptide, ularitide, which is a synthetic analogue of urodilatin, a naturally occurring natriuretic and vasodilator hormone produced by the kidneys and discovered by W.G. Forssmann [19], the son of the Nobel prize-winner for cardiac catheterisation, Werner Forssmann [20]. Ularitide has been developed on the basis of the exciting results with urodilatin in uncontrolled trials, and is currently being tested in

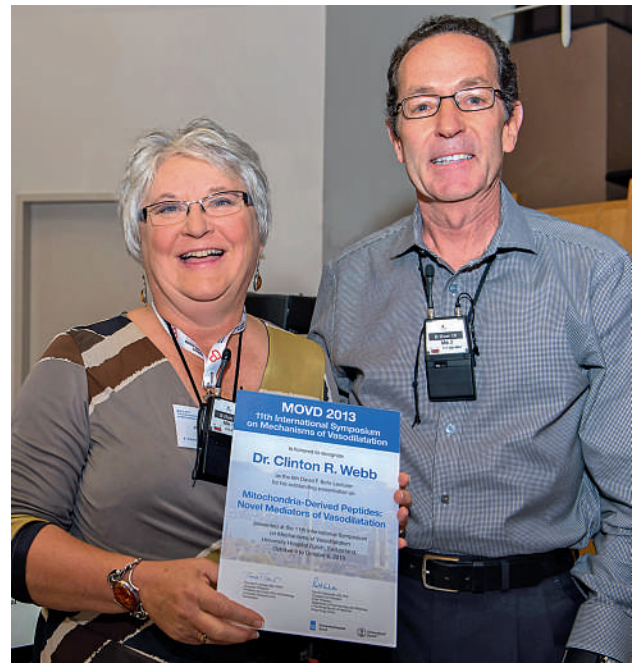


Figure 4

The David Bohr Lecturer Clinton R. Webb from Augusta, USA, with the chairman of the session, Virginia Miller of the Mayo Clinic, USA. With this lecture the work of the late David Bohr, an eminent vascular physiologist who contributed to our understanding of vascular smooth muscle tone at the University of Ann Arbor, Michigan, is remembered.

a large Phase III multicentre study including more than a thousand patients with acute heart failure.

The session on novel vasoactive peptides was complemented by the *David Bohr Lecture* (fig. 4), by Clinton R. Webb from Augusta, USA, who gave a talk on "Mitochondria-derived peptides: novel mediators of vasodilation" [21]. Dr Bohr was one of the pioneers who investigated the function of vascular smooth muscle cells, and, in particular, established the key role of changes in intracellular Ca^{2+} concentration in their relaxation and contraction. Of note, mitochondria contain N-formyl peptides that activate specific receptors, leading to profound vasodilatation. Such a mechanism appears to be particularly important in septic shock, and the discovery of this pathway, which can be inhibited by cyclosporin-H, is likely to provide novel opportunities to treat this devastating condition, which still has a mortality rate of 30% to 50%. A more elaborate version of his talk will appear as a review article in the *European Heart Journal* in 2014 [20].

Vascular adaptation in hypertension

Ernesto L. Schiffrin, an eminent clinician and hypertension researcher from the Jewish General Hospital in Montreal, Canada, had been invited to give the *Björn Folkow Lecture* on growth and remodelling (fig. 5). Björn Folkow, Professor of Physiology at Göteborg

University in Sweden, was an eminent physiologist who discovered the importance of structural changes of the resistance arteries during the development and aggravation of hypertension. His work is commemorated with this lecture, which is given by researchers who have during their lifetime contributed significantly to the field of hypertension research.

Ernesto L. Schiffrin talked on the “Effects of immune mechanisms on the vasculature in hypertension” and demonstrated in his elegant talk that T regulatory lymphocytes contribute importantly to inflammatory responses in small resistance arteries in hypertension and, therefore, may aggravate and/or sustain hypertension by interfering with the L-arginine / nitric oxide pathway and by expressing endothelin. The role of endothelin [22] in the control of vascular tone was then reviewed by both Paul M. Vanhoutte and Thomas F. Lüscher, who emphasised that this peptide is normally suppressed by biologically active nitric oxide via a cyclic guanine monophosphate-dependent mechanism, but widely expressed in situations of endothelial dysfunction [23, 24, 25]. Disturbances of the L-arginine / nitric oxide pathway lead to increased expression, release and action of the peptide in the vasculature and in the circulation. Therefore, endothelin contributes to different forms of hypertension, in particular deoxycorticosterone acetate-salt hypertension, Dahl-salt hyper-

tension [26] and angiotensin II-induced hypertension [27]. Of note, angiotensin II stimulates endothelin production and hence endothelin markedly contributes to any condition where the renin angiotensin system is activated [28]. Although, bosentan has been shown by Henry Krum [29] to lower blood pressure in a manner similar to enalapril, this drug, as well as other molecules interfering with endothelin receptors, have not been further developed in hypertension for several reasons. One of them is that in endothelin receptor knock-out animals, malformations develop in the jaw and throat [30]. Thus, any use of such molecules in females of childbearing age is precluded. Furthermore, headaches associated with these drugs, particularly in hypertensive patients, also made their development less attractive.

On the other hand, the activity of the endothelin system is markedly elevated in patients with heart failure, in particular in those with cardiogenic shock [31]. Furthermore, after acute myocardial infarction, a condition often leading eventually to heart failure, baseline endothelin levels are highly predictive of future outcome [32]. In spite of that, and although endothelin receptor antagonists had very favorable haemodynamic effects in patients with heart failure [33, 34], both the EARTH-trial [35] and the ENABLE-trial [36] found no difference in remodelling and clinical outcome, respectively. Therefore, endothelin receptor antagonists have not been further considered for the treatment of heart failure, another example of a molecular lost in translation in this condition [37].

Eventually, it appears that endothelin receptor antagonists are particularly efficacious in pulmonary hypertension of different causes and, indeed, has been shown to lower morbidity and mortality in large outcome trials [38]. Finally, endothelin may play a role in Takotsubo syndrome where plasma levels of endothelin are increased owing to a down-regulation of the regulating messenger ribonucleic acid (mRNA) [39]. However, effects of endothelin antagonists in this condition have not yet been evaluated.

Endothelium-dependent hypoxic contractions

Several decades ago, it had already been noted that blood vessels exposed to low oxygen tension exhibit contractions. As shown by Gabor Rubanyi and Paul M. Vanhoutte [40], such contractions involve the transfer of an endothelium-derived mediator in the canine coronary artery. Paradoxically, the mediator in question appears to be nitric oxide, which activates soluble guanylyl cyclase [41]. The mechanism involved remained elusive until Yuasheng Gao reported at the symposium that hypoxia causes the latter enzyme to switch substrates and produce cyclic inosine monophosphate, which turns out to be a new second messenger causing coronary vasoconstriction.



Figure 5

The Björn Folkow Lecture on growth and remodelling was given by Ernesto Schiffrin from McGill Montréal, Canada. With this lecture, chaired this year by Paul M. Vanhoutte, the enormous contributions of the late Björn Folkow to the field of structural vascular adaptation of the resistance arteries in hypertension is remembered.

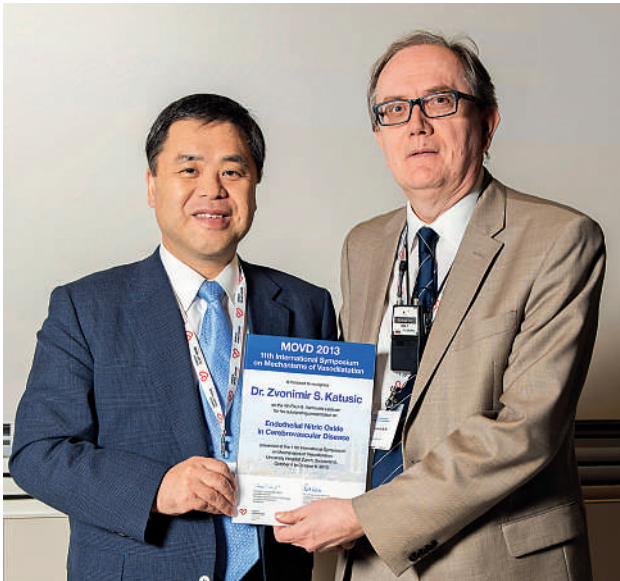


Figure 6 The 4th Paul M. Vanhoutte Lecturer on vascular pathology, Zvonimir S. Katusic from the Mayo Clinic, USA, was introduced by Hiroaki Shimokawa from Sendai University, Japan, for his contributions to the regulation of the cerebrovascular circulation.

Endothelial function in the cerebral circulation

On the last day, Zvonimir S. Katusic from the Mayo Clinic, in Rochester, Minnesota, gave the 4th *Paul M. Vanhoutte Lecture* on vascular pathology (fig. 6). His lecture on “Endothelial nitric oxide in cerebrovascular disease” revealed truly novel aspects of the role of nitric oxide in Alzheimer’s disease as a regulator of the processing of the amyloid precursor protein to Ab3, a crucial pathway in the development of Alzheimer’s disease. Of note, endothelial nitric oxide knockout mice develop neurological alterations compatible with a certain form of Alzheimer’s disease, suggesting that this mechanism may be indeed also be operative and important *in vivo*. Whether such mechanisms are important also in humans prone to or those who have already developed Alzheimer’s disease remains to be determined.

Conclusion

Thus, the 11th International Symposium on Mechanisms of Vasodilatation again provided vascular science of the highest level and allowed insights into the current state-of-the-art of this important field of vascular biology, relevant not only for scientists but also for clinicians.

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