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EDITORIAL

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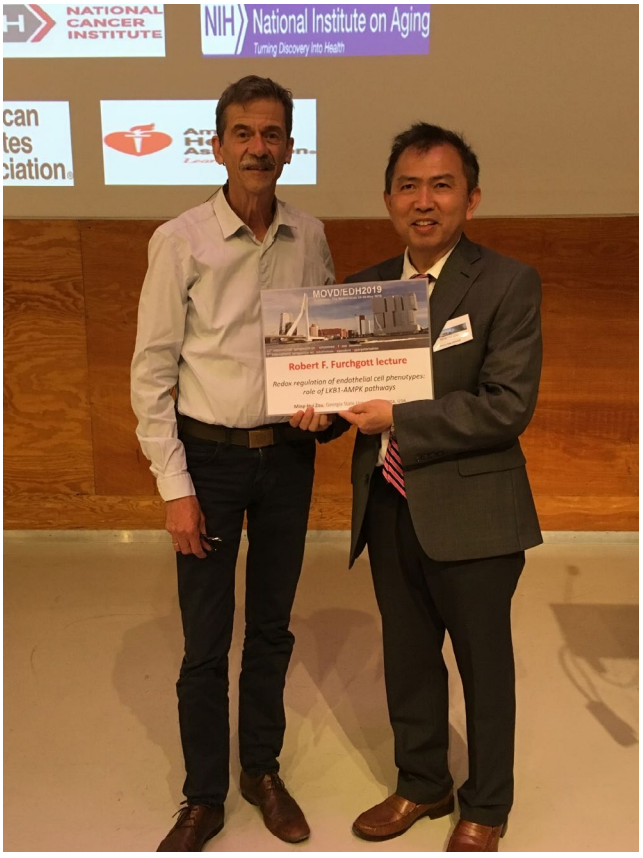
Mechanisms of Vasodilatation/Endothelium-dependent Hyperpolarization (MOVD/EDH) 2019—Rotterdam, The Netherlands

Jan Danser and Paul Vanhoutte



Jo De Mey and Min-Hui Zou

Mark Chapleau, Paul Vanhoutte, Steven Segal and Brant Isakson

Ulf Simonsen and Yu Wang

Paul M. Vanhoutte initiated the first international symposium on the Mechanisms of Vasodilatation (MOVD) in Antwerp in 1977. This was to be followed by a series of MOVD meetings held all over the world (Table 1). Not only nitric oxide, but also endothelium-dependent hyperpolarization (EDH), was extensively discussed during these meetings, and soon separate EDH meetings were organized in parallel, the majority of them in France (Table 2). After 12 MOVD meetings and 7 EDH meetings, in 2019, the two were combined for the first time in Rotterdam, The Netherlands (20-22 May). There were around 90 participants. Sadly, it turned out to be the last meeting that Paul Vanhoutte could attend, since he passed away on 23 August 2019. As always, he was sitting on the front row and stimulating every speaker with multiple thoughtful questions. He also provided what he called his swan song, entitled "NO, from good to bad". Unfortunately, he was correct. In this talk, he described that the well-known enhanced contractions after hypoxia also involve endothelial NO, yet instead of being a vasorelaxant agent acting via guanosine-3′,5′-cyclic monophosphate (cyclic GMP), now causing constriction by stimulating biased activity of soluble guanylyl cyclase, resulting in the generation of inosine-3′,5′-cyclic monophosphate (cyclic IMP).[1]

In addition, 6 invited speakers provided lectures named after giants in the vascular field. In the *Robert F Furchgott* lecture, Min-Hui Zou (Atlanta, USA) discussed how adenosine monophosphate-activated protein kinase, a sensor of redox status, results in vascular disease when dysfunctional. Rhian Touyz (Glasgow, UK) gave the *David F Bohr* lecture. She introduced the novel reactive oxygen species–generating Nox 5 and its role in vascular smooth muscle cells (VSMC). Claire Peppiatt-Wildman (Kent, UK), providing the *Björn Folkow* lecture, revealed to what extent pericytes in renal capillaries mimic VSMC, displaying

TABLE 1 MOVD meetings since 1977

Year	Location	Organizers
1977	Wilrijk, Belgium	PM Vanhoutte and I Leusen
1980	Wilrijk, Belgium	PM Vanhoutte and I Leusen
1983	Sydney, Australia	PM Vanhoutte and S Vatner
1986	Rochester, USA	PM Vanhoutte
1989	Strasbourg, France	JC Stoclet and PM Vanhoutte
1993	Glasgow, United Kingdom	I McGrath and PM Vanhoutte
1997	Maastricht, The Netherlands	JGR De Mey and PM Vanhoutte
2001	Boston, USA	RA Cohen and PM Vanhoutte
2005	Wilrijk, Belgium	A Herman and PM Vanhoutte
2009	Sendai, Japan	H Shimokawa and PM Vanhoutte
2013	Zurich, Switzerland	TF Lüscher and PM Vanhoutte
2016	Rochester, USA	VM Miller, RC Webb and PM Vanhoutte
2019	Rotterdam, The Netherlands	AHJ Danser, JGR De Mey, U Simonsen, BE Isakson and PM Vanhoutte
2021	Hong Kong, China	Y Wang, S Leung, Y Huang, AHJ Danser, JGR De Mey and RE Widdop

Note: The 2019 meeting was a joint MOVD/EDH meeting.

TABLE 2 EDH meetings since 1995

Year	Location	Organizers
1995	Vaux de Cernay, France	M Félétou and PM Vanhoutte
1998	Vaux de Cernay, France	M Félétou and PM Vanhoutte
2000	Vaux de Cernay, France	M Félétou and PM Vanhoutte
2002	Vaux de Cernay, France	M Félétou and PM Vanhoutte
2008	Tampere, Finland	E Moilanen, I Pörsti, H Vapaatalo and PM Vanhoutte
2012	Vaux de Cernay, France	M Félétou and PM Vanhoutte
2015	Nyborg, Denmark	JGR De Mey, P Hansen and PM Vanhoutte
2019	Rotterdam, The Netherlands	AHJ Danser, JGR De Mey, U Simonsen, BE Isakson and PM Vanhoutte

Note: Initially, this meeting was known as endothelium-derived hyperpolarizing factor (EDHF) meeting. The 2019 meeting was a joint MOVD/EDH meeting.

among others relaxant responses to NO and constrictor responses to endothelin-1. In her *Paul M Vanhoutte* lecture, Yu Wang (Hong Kong, China) suggested that the pro-inflammatory molecule lipocalin-2 (also known as neutrophil gelatinase-associated lipocalin) contributes to obesity-associated pathologies and may thus be a novel drug target.[2] The lecture named after *John T Shepherd* (born on 21 May 1919, ie exactly 100 years before this meeting) was given by Mark Chapleau (Iowa City, USA). He focused on mechanoelectrical transduction, particularly in relation to the baroreceptor reflex and discussed novel roles for hydrogen peroxide and the PIEZO channels in baroreceptor activity. Finally, the lecture linked to EDH (named after *Tudor Griffith*) was given by Steven Segal (Columbia, USA) who illustrated how hyperpolarization is conducted along the endothelium and into surrounding VSMC via gap junctions, while ion channels activated by oxidative stress or the sympathetic nervous system counterbalance this phenomenon.

Three symposia were devoted, respectively, to *ageing*, *pre-eclampsia* and *gender aspects*. Ageing VSMC change their phenotype from contractile to synthetic and osteochondrocytic, hence the greater risk of vascular calcification in the elderly. Defective maturation of laminin A, normally responsible for nuclear pore formation and chromatin organization, results in pre-laminin A accumulation, which induces DNA damage, apoptosis and senescence (Catherine Shanahan, London, UK). Removing senescent cells with senolytic drugs increases a healthy life span (Darren Baker, Rochester, USA),[3] while reduced activity of DNA repair enzymes does the opposite (Anton Roks, Rotterdam, The Netherlands).[4] The mitochondrial adaptor protein p66(Shc) and the deacetylating sirtuins additionally regulate the ageing process, while endothelial NO synthase contributes by generating reactive oxygen species (Thomas Lüscher, London, UK).[5]

Ravi Thadhani (Los Angeles, USA) discussed the angiogenic imbalance in pre-eclampsia, resulting from the placental release of the soluble receptor, soluble fms–like tyrosine kinase (sFlt)-1, which binds and inactivates vascular endothelial growth factor (VEGF). Given the important vascular and renal effects of VEGF, this results in endothelial dysfunction, endothelin-1 up-regulation, hypertension and proteinuria. Not surprisingly, VEGF inhibitors used in cancer patients exert the same effects (Katrina Mirabito Colafella, Melbourne, Australia).[6] Novel therapies for pre-eclampsia are now aimed at either removing sFlt-1 or inhibiting endothelin-1. Sandra Davidge (Edmonton, Canada) provided evidence for an additional role for lectin-like oxidized LDL receptor-1 in the sFlt-1 up-regulation.

Virginia Miller (Rochester, USA) stressed the importance of stratifying one's experiments according to sex, given the multiple male/female differences. Ultimately, this may imply that men and women require different drugs and/or different doses. Yet, Peter Bie (Odense, Denmark) warned that we should not forget our original research goal, which may well be sex-independent, and thus adding sex as an additional parameter would at most complicate things and increase animal numbers unnecessarily.[7] Hester den Ruijter (Utrecht, The Netherlands), making use of the adverse drug reaction (ADR) database of Uppsala Monitoring Centre (currently containing 19 million ADR reports!), revealed that women report more ADRs, with men predominantly reporting serious ADRs. The difference is, therefore, due to less serious ADR. Whether this implies that women experience more ADR cannot yet be concluded from these data. Finally, Susan Leung (Hong Kong, China) explained how oestradiol up-regulates both NO- and EDH-type relaxations and was able to link this to male/female vascular responsiveness differences in aged and diseased animals.

The remainder of the programme consisted of approximately 50 free communications, either as poster or oral

presentation. This issue contains the papers that were submitted by the invited speakers and three additional abstract presenters.[8-10]

The next MOVD meeting will be held in fond memory of Paul M. Vanhoutte in his "own" university city (since 2006) Hong Kong (http://movd2021.hku.hk), where he remained permanent Visiting Professor until his death.

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REFERENCES

1. Vanhoutte PM, Leung SWS. Hypoxic augmentation: the tale of a strange contraction. *Basic Clin Pharmacol Toxicol* 2019.
2. Li D, Yan Sun W, Fu B, Xu A, Wang Y. Lipocalin-2-The myth of its expression and function. *Basic Clin Pharmacol Toxicol* 2019.
3. Graves SI, Baker DJ. Implicating endothelial cell senescence to dysfunction in the ageing and diseased brain. *Basic Clin Pharmacol Toxicol* 2020.
4. Golshiri K, Ataei Ataabadi E, Portilla Fernandez EC, Jan Danser AH, Roks AJM. The importance of the nitric oxide-cGMP pathway in age-related cardiovascular disease: focus on phosphodiesterase-1 and soluble guanylate cyclase. *Basic Clin Pharmacol Toxicol* 2019.
5. Liberale L, Kraler S, Camici GG, Lüscher TF. Aging and longevity genes in cardiovascular diseases. *Basic Clin Pharmacol Toxicol* 2020.
6. Mirabito Colafella KM, Neuman RI, Visser W, Danser AHJ, Versmissen J. Aspirin for the prevention and treatment of pre-eclampsia: a matter of COX-1 and/or COX-2 inhibition? *Basic Clin Pharmacol Toxicol* 2019.
7. Bie P, Debrabant B. Gonadal sex and animal experimentation: Perfection vs. 3R principle? *Basic Clin Pharmacol Toxicol*. 2020.
8. Chen H, Vanhoutte PM, Leung SWS. Vascular adenosine monophosphate-activated protein kinase: enhancer, brake or both? *Basic Clin Pharmacol Toxicol* 2019.
9. Chen H, Simonsen U, Aalkjaer C. A sex-specific, COX-derived thromboxane-receptor activator causes depolarization and vasoconstriction in male mice mesenteric resistance arteries. *Basic Clin Pharmacol Toxicol.* 2020.
10. Shimokawa H, Godo S. Nitric oxide and endothelium-dependent hyperpolarization mediated by hydrogen peroxide in health and disease. *Basic Clin Pharmacol Toxicol* 2019.