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IM - COMMENTARY

# Is circulating endothelin evaluation useful for clinicians?

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"I start in the middle of a sentence and move both directions at once."

John Coltrane, 1926–1967.

When John Coltrane generated a distinctive and enthralling sound due to his unbelievable ability to play various notes at once amid gorgeous cascades of scales, he explained that giant leap by the above sentence [1].

The Coltrane' sentence perfectly applies to endothelin-1, a peptide of 21 amino acids in length with uniquely long-lasting vasoconstrive effects [2]. Once discovered by Yanagisawa et al. [3], it seemed to most of us that the vascular endothelium had acquired the pole position among regulating systems of the vascular tone, making of endothelin-1 the strongest contributing agent to the pathogenesis of hypertension, atherosclerosis, and vascular spasm (Fig. 1). In the following years, despite a number of studies aiming to better define the endothelin-1 role and to develop specific therapeutic strategies in various patients' settings [4, 5], plasma endothelin-1 measurement was remained irrelevant in the diagnostic work-up of cardiovascular diseases [2]. Similarly, although often and beneficially used in various diseases, such as pulmonary hypertension, the inhibition of endothelin-receptor subtypes did not reach the expected position in most of the common cardiovascular disorders such as hypertension, coronary heart disease, stroke, and heart failure [2]. Thus, the endothelin music—in the third millennium—started from a stirring sentence, but the expected number of successful and wonderful cascades of scales was rarely observed.

In this context, the paper published in this issue by Moroni and co-workers [6] is of extreme interest and revitalises the interest around circulating endothelin-1. In particular, authors investigated the main peptide belonging to the endothelin axis, i.e., endothelin-1, in two groups of normotensives, the first without evidence of myocardial ischemia despite chest pain (i.e., the control group) and the second with stable angina and angiographically relevant coronary stenosis. Furthermore, circulating endothelin-1 level was also assessed in hypertensive patients with chest pain but no evidence of myocardial ischemia and hypertensives patients with stable angina and angiographically relevant coronary stenosis. Of note, plasma endothelin-1 concentration was assessed before and after dipyridamole administration. Responses of circulating endothelin-1 levels were totally divergent between hypertensive and normotensive subgroups, the first reporting the highest increments in endothelin-1 after dipyridamole but only in patients manifesting with angiographically relevant coronary heart disease. The interaction between hypertension and coronary artery disease in promoting endothelin-1 release was further supported by the modest, although significant increment in circulating endothelin-1 concentrations that was observed in patients with evident coronary artery disease, but no hypertension as well as in those with hypertension, but no angiografically relevant stenosis of the coronary bed.

The study by Moroni et al. [6], as it is correctly stated by the authors, has several limitations, lacking of the evaluation of endothelin-1 at the heart level and/or in coronary veins. Moreover, the study population was substantially small in all of its four subgroups, while only mature endothelin-1 was measured. Thus, it is impossible to speculate on the effective role of endothelin-1 and the whole endothelin axis in promoting myocardial ischemia. In turn, it is not possible to affirm that the observed increment in circulating endothelin-1 was the direct consequence of the response to dipyridamole.

Despite the above limitations, it is evident from the nice paper by Moroni et al. [6] that a linkage did exist between hypertension and ischemic heart disease in promoting endothelin-1 overproduction. Concordant to this, antagonism of the endothelin receptor by the dual antagonist bosentan [7] and the mildly selective $ET_A$ receptor darusentan [8] gave raise to some doubts on their possible use in human hypertension. However, when endothelin antagonism was

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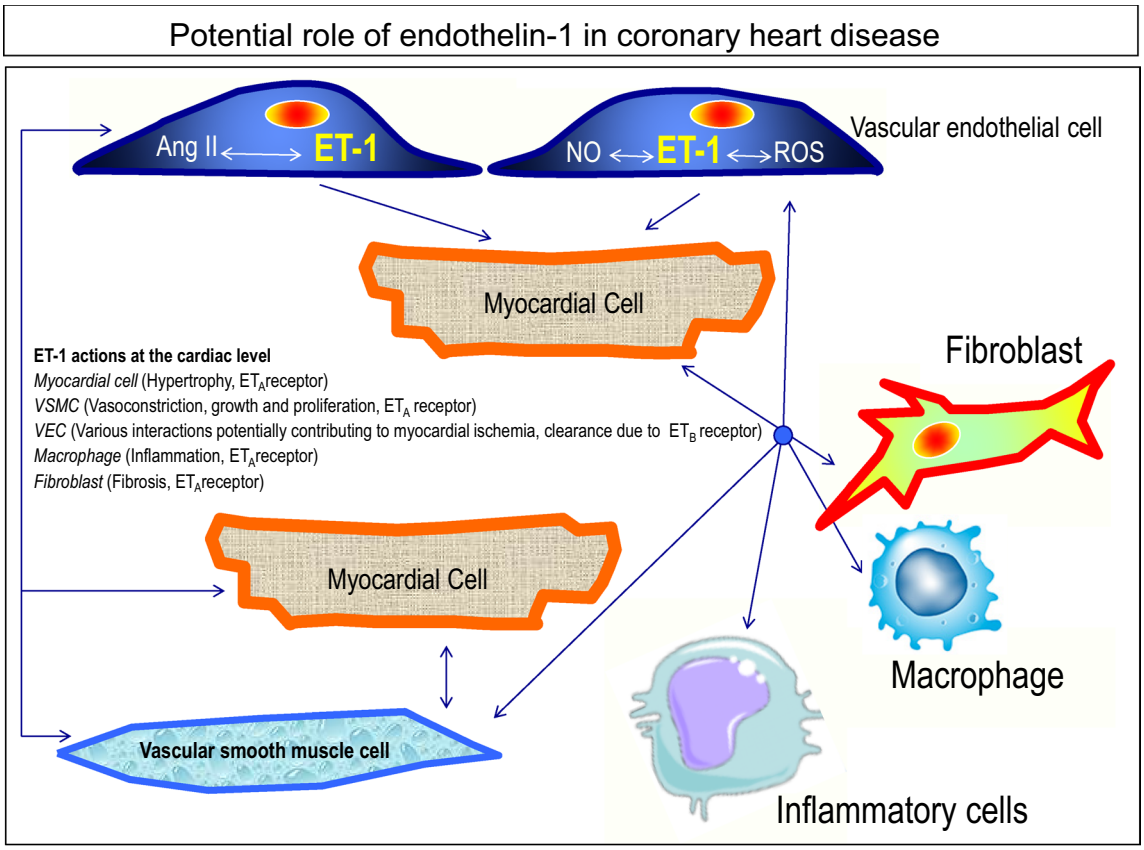


**Fig. 1** Potential role of endothelin-1 at the heart level. *Ang II* angiotensin II, *ET-1* endothelin-1, *NO* nitric oxide, *ROS* reactive oxygen species, *VEC* vascular endothelial cell, *VSMC* vascular smooth muscle cell

used in treatment-resistant hypertension, darusentan administration was followed by attractive results in term of effective blood pressure reduction in the DORADO trials [9, 10]. Thus, aprocitentan, i.e., the active metabolite of macitentan, was tested in a phase II study conducted in 490 essential hypertensive patients with demonstrated resistance to antihypertensive therapy [11]. Results were promising and the multicentre PRECISION phase III trial is still ongoing in a larger study population [12]. Therefore, a strong rationale seems to link hypertension with the endothelin system and supports the use of endothelin-1 selective antagonists in a high-risk condition such as treatment-resistant hypertension. In contrast to this, the role of the endothelin system in ischemic cardiomyopathy is still debated. Endothelin-1 is secreted abluminally with suggested paracrine actions on the myocardial cell [13]. Of note, the most active peptide of the renin–angiotensin–aldosterone axis, i.e., angiotensin II, can induce endothelin-1 expression in endothelial cells [14]. In turn, endothelin-1 seems to be able to potentiate the vascular effects of angiotensin II [14] making it conceivable that the endothelin axis might simultaneously favour hypertension and coronary atherogenesis. On the other hand, the role of endothelin-1 as marker of either acute or chronic vascular endothelial damage has been already recognized [4]. Thus, it is also reasonable to speculate that—in the presence of hypertension—acute coronary ischemia might induce a marked extra-increment of endothelin-1 release into the bloodstream. In this regard, the hypothesis by Moroni et al. [6], i.e., that an increased release of mature endothelin-1 might represent a compensatory mechanism, aiming to maintain distal blood flow delivery in ischemic territories, is extremely fascinating. Although impossible to demonstrate by an in vivo study such as that published in this Journal issue [6], the role of the endothelin axis in inducing hypertension and coronary artery disease is strongly supported by the divergent behaviour observed in the four evaluated subgroups.

Thus, in summary, we do agree with authors that the history of endothelin-1 and its antagonism is still to be written in various clinical settings. Only apparently prone to a premature death, the interest upon endothelin-1 is still alive and awaits to start from the middle of a sentence and follow various pathways [1]. Pathophysiologic studies and clinical trials are then necessary to reinforce the very interesting suggestion deriving from the paper by Moroni et al. [6].

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Statements on human and animal rights** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** None.

## References


1. Porter L (2006) Blue Trane. La vita e la musica di John Coltrane Minimum Fax (eds.), EAN: 9788875211158, p 575
2. Dhaun N, Webb DJ (2019) Endothelins in cardiovascular biology and therapeutics. Nat Rev Cardiol. https://doi.org/10.1038/s41569-019-0176-3
3. 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(6163):411–415.
4. 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; Working Group on Endothelin and Endothelial Factors of the European Society of Hypertension. 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. 2005; 23(1):7–17
5. Ferri C, Properzi G, Tomassoni G, Santucci A, Desideri G, Giuliani AE, Starling RC, Ratliff NB, Cook DJ, McCarthy P, Young JB, Yamani MH (2002) Patterns of myocardial endothelin-1 expression and outcome after cardiac transplantation. Circulation 105(15):1768–1771
6. Moroni C, Tolone S, Bondanini F, Schillaci O, Affricano C, Cassone R, Gaspardone A, Gaudio C (2019) Endothelin-1 in hypertensive patients with ischemic heart disease. Intern Emerg Med. https://doi.org/10.1007/s11739-019-02095-3
7. Krum H, Viskoper RJ, Lacourciere Y, Budde M, Charlon V (1998) The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. N Engl J Med 338:784–790
8. Nakov R, Pfarr E, Eberle S (2002) Darusentan: an effective endothelin A receptor antagonist for treatment of hypertension. Am J Hypertens 15:583–589
9. Webb DJ (2010) DORADO: opportunity postponed: lessons from studies of endothelin receptor antagonists in treatment-resistant hypertension. Hypertension 56:806–807
10. Bakris GL (2010) Divergent results using clinic and ambulatory blood pressures: report of a darusentan resistant hypertension trial. Hypertension 56:824–830
11. Idorsia. Drug discovery & clinical development (2019) idorsia https://www.idorsia.com/documents/com/fact-sheets-presentations/fs-clinical-development.pdf
12. US National Library of Medicine (2019) ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT02603809
13. Segers VF, Gevaert AB, Boen JR, Van Craenenbroeck EM, De Keulenaer GW (2019) Epigenetic regulation of intercellular communication in the heart. Am J Physiol Heart Circ Physiol. https://doi.org/10.1152/ajpheart.00038.2019
14. Yu L, Yang G, Weng X, Liang P, Li L, Li J, Fan Z, Tian W, Wu X, Xu H, Fang M, Ji Y, Li Y, Chen Q, Xu Y (2015) Histone methyltransferase SET1 mediates angiotensin II–induced endothelin-1 transcription and cardiac hypertrophy in mice. Arterioscler Thromb Vasc Biol 35:1207–1217


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