

Endothelial Progenitors and Blood Microparticles: Are They Relevant to Heart Failure With Preserved Ejection Fraction?

Shantsila, Eduard; Lip, Gregory Y.h.

DOI:

[10.1016/j.ebiom.2016.01.025](https://doi.org/10.1016/j.ebiom.2016.01.025)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Shantsila, E & Lip, GYH 2016, 'Endothelial Progenitors and Blood Microparticles: Are They Relevant to Heart Failure With Preserved Ejection Fraction?', *EBioMedicine*, vol. 4, pp. 5-6.

<https://doi.org/10.1016/j.ebiom.2016.01.025>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Accepted Manuscript

Endothelial Progenitors and Blood Microparticles: Are They Relevant to Heart Failure with Preserved Ejection Fraction?

Eduard Shantsila, Gregory Y.H. Lip

PII: S2352-3964(16)30021-4
DOI: doi: [10.1016/j.ebiom.2016.01.025](https://doi.org/10.1016/j.ebiom.2016.01.025)
Reference: EBIOM 452

To appear in: *EBioMedicine*

Received date: 18 January 2016
Accepted date: 18 January 2016



Please cite this article as: Shantsila, Eduard, Lip, Gregory Y.H., Endothelial Progenitors and Blood Microparticles: Are They Relevant to Heart Failure with Preserved Ejection Fraction?, *EBioMedicine* (2016), doi: [10.1016/j.ebiom.2016.01.025](https://doi.org/10.1016/j.ebiom.2016.01.025)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

To accompany paper by Berezin et al.

EBIOM-D-15-00487R1

COMMENTARY

**Endothelial Progenitors and Blood Microparticles: Are They Relevant to Heart
Failure with Preserved Ejection Fraction?**

Eduard Shantsila	PhD	Postdoctoral Research Fellow
Gregory YH Lip	MD	Professor of Cardiovascular Medicine

University of Birmingham Institute of Cardiovascular Sciences
City Hospital, Birmingham B18 7QH
England, UK

Correspondence to:

Professor Gregory YH Lip

Tel: +44 121 554 3801; Fax: +44 121 554 4083; g.y.h.lip@bham.ac.uk

Key words

Heart failure, heart failure with preserved ejection fraction, endothelial progenitor cells, microparticles

Heart failure (HF) with preserved ejection fraction (HFpEF) has emerged as a major problem of modern cardiology. In contrast to HF with systolic impairment advances in management of HFpEF have been humble and there is lack of proven effective treatment to improve longevity and reduce disability in such patients. Futility of the medications established in systolic HF to help subjects with HFpEF reflects difference in the pathophysiological mechanisms of the two forms of HF. Good understanding of these mechanisms is essential for discovery of new treatments in the future.

The numbers of endothelial progenitor cells (EPCs) are upregulated in systolic HF and their numbers correlate with levels of various cytokines, such as tumor necrosis factor- α .¹ However EPCs counts vary depending on the stage of HF with relatively higher levels seen in mild or well-controlled disease but the numbers decrease progressively in advanced HF stages.¹

Hypertension is a major cause of HFpEF as opposed to ischemia in systolic HF. Diastolic dysfunction and abnormal cardiac stiffness are recognized factors predisposing to the development of HFpEF in patients with high blood pressure.² Hypertension is related to impairment of EPC migratory capacity in vitro. This may be partly explained by upregulation of angiotensin II, a molecule shown to reduce telomerase activity in EPCs and to accelerate their senescence.³

Circulating microparticles have been appreciated as an important component of intercellular communication.^{4, 5} They may be involved in more complex regulatory pathways due to their capacity to deliver multiple molecules in the same lipid envelope and to specifically target particular types of cells using their surface

receptors. Patients with hypertension and systolic HF have abnormal levels of different types of blood microparticles but data on microparticles in HFpEF are scarce.

EPCs are diverse and they embrace cells of different progeny.⁶ Two types of EPCs appear to be of particular relevance. ‘Late’ EPCs are extremely scarce in circulation and they most likely represent cells resident within the endothelium. When appropriately stimulated they have immense proliferative capacity and can give origin to endothelial cells per se. However, their assessment is limited but the requirement for long-term in vitro culture experiments. The other major type of EPCs are so called ‘early’ EPCs, which produce numerous endothelial like cells within few days of in vitro culture. They have been shown to be predominantly of monocytic origin and they contribute to angiogenesis by releasing appropriate cytokines, chemokines, growth factors, etc., thus orchestrating mobilization of other cell types and modulating activity of the tissue resident cells. Given the monocytic origin of these cells they can be assessed by flow cytometry from fresh blood samples. This opportunity has been utilized Berezin et al. in their study published in this issue of *EBioMedicine*.⁷

Berezin et al. have demonstrated significant differences in the pattern of circulating EPCs and endothelial microparticles in patients with HF with reduced or preserved ejection fraction.⁷ The study provides several interesting observations. Among the different EPC phenotypes assessed, only CD14⁺ cells (i.e., cells of monocytic origin) were independently associated with HFpEF. This accords with extensive and ongoing cardiac remodeling in patients with HFpEF.

However detailed relationship between the tested parameters and measures of cardiac remodeling and outcomes were beyond the scope of the present study and need to be established in the future in prospective trials. Such information is essential to establish whether the tested pathways could produce clinically relevant therapeutic targets.

Of interest, in the study by Berezin et al. HFpEF was related to upregulation of monocytes with angiogenic phenotype rather than cells with 'classical' CD34+CD309+ EPC phenotype.^{7, 8} This fits well in the progressively better-understood role of a specific monocyte population (i.e., 'intermediate' or Mon2 subset) in pathogenesis and prognostication in several cardiac disorders including HF. In fact, this subset has been shown to have highest of all monocytes expression of CD309, Tie-2 and a range of other receptors involved in angiogenesis and tissue remodeling.⁹ The results obtained by Berezin et al also correspond to recent observations that non-monocytic circulating EPCs can in fact be downregulated in HFpEF compared to controls without HF thus highlighting the importance of careful characterization of specific phenotype of cells assessed under generic term of EPCs.¹⁰

Berezin et al. show that changes in proportions of certain types of microparticles (CD31+ could be shed from both endothelial cells and platelets) and angiogenic monocytes are linked to the type of HF.⁷ It is possible that these changes are secondary to the degree of the background ischemia or shifts in cardiac and vascular hemodynamics associated with particular HF form (for example, increased endothelial shear stress in hypertension). However it can also reflect poorly understood aspects of endothelial dysfunction. Indeed, whilst the role of endothelial

dysfunction is well-established magnitude and nature of endothelial changes in HFpEF is less clear.

Extensive experimental work is also warranted to identify and describe the whole length of the pathophysiological pathways implicated in the processes mediated by angiogenic monocytes and microparticles. This will help to determine the key components of the pathways, which will help to modulate them in the desired direction.

The study does not answer the question of whether the observed upregulation of biomarkers is involved in the development of HFpEF or they reflect a mechanism aiming to contrabalance the pathogenic factors or to promote adaptation of the cardiovascular system to hemodynamic changes. These questions will need to be answered in the future. Overall the study by Berezin and colleagues provides new insight in processes differentiating HFpEF and systolic HF and it leads to a string of interesting hypotheses to be tested in the future.

Conflicts of interest:

The authors declared no conflicts of interest.

REFERENCES

1. Valgimigli M, Rigolin GM, Fucili A, Porta MD, Soukhomovskaia O, Malagutti P, Bugli AM, Bragotti LZ, Francolini G, Mauro E, Castoldi G and Ferrari R. CD34+ and endothelial progenitor cells in patients with various degrees of congestive heart failure. *Circulation*. 2004;110:1209-12.
2. Komajda M and Lam CS. Heart failure with preserved ejection fraction: a clinical dilemma. *European heart journal*. 2014;35:1022-32.
3. Imanishi T, Hano T and Nishio I. Angiotensin II accelerates endothelial progenitor cell senescence through induction of oxidative stress. *Journal of hypertension*. 2005;23:97-104.
4. Geddings JE and Mackman N. New players in haemostasis and thrombosis. *Thrombosis and haemostasis*. 2014;111:570-4.
5. Shantsila E, Montoro-Garcia S, Gallego P and Lip GY. Circulating microparticles: challenges and perspectives of flow cytometric assessment. *Thrombosis and haemostasis*. 2014;111:1009-14.
6. Shantsila E, Watson T and Lip GY. Endothelial progenitor cells in cardiovascular disorders. *Journal of the American College of Cardiology*. 2007;49:741-52.
7. Berezin A, Kremzer A, Martovitskaya Y, Berezina T and Gronenko E. Pattern of endothelial progenitor cells and apoptotic endothelial cell-derived microparticles in chronic heart failure patients with preserved and reduced left ventricular ejection fraction. *EBioMedicine*. 2016; doi:10.1016/j.ebiom.2016.01.018.
8. Cesari F, Marcucci R, Gori AM, Burgisser C, Francini S, Roberts AT, Sofi F, Gensini GF, Abbate R and Fattiroli F. Adherence to lifestyle modifications after a

cardiac rehabilitation program and endothelial progenitor cells. A six-month follow-up study. *Thrombosis and haemostasis*. 2014;112:196-204.

9. Shantsila E, Wrigley B, Tapp L, Apostolakis S, Montoro-Garcia S, Drayson MT and Lip GY. Immunophenotypic characterization of human monocyte subsets: possible implications for cardiovascular disease pathophysiology. *Journal of thrombosis and haemostasis : JTH*. 2011;9:1056-66.

10. Chiang CH, Huang PH, Leu HB, Hsu CY, Wang KF, Chen JW and Lin SJ. Decreased circulating endothelial progenitor cell levels in patients with heart failure with preserved ejection fraction. *Cardiology*. 2013;126:191-201.