ESC European Society of Cardiology

European Heart Journal (2018) **39**, 2398–2400
doi:10.1093/eurheartj/ehy300

EDITORIAL

Gut microbiome composition, a third player in the inflammation–arterial stiffness relationship

Stéphane Laurent[1]* and Rosa Maria Bruno[2]

[1]Department of Pharmacology, European Georges Pompidou Hospital, Assistance Publique-Hôpitaux de Paris, PARCC INSERM UMR 970 and University Paris Descartes, Paris, France; and [2]Department of Clinical and Experimental Medicine, University of Pisa, and Institute of Clinical Physiology, CNR, Pisa, Italy

Online publish-ahead-of-print 31 May 2018

This editorial refers to 'Gut microbial diversity is associated with lower arterial stiffness in women'†, by C. Menni *et al.*, on page 2390.

The growing interest in the clinical measurement of arterial stiffness comes from the repeated demonstration that arterial stiffness has predictive value for cardiovascular (CV) events.[1,2] The measurement or arterial stiffness through carotid–femoral pulse wave velocity (PWV) is generally considered as an index of early vascular ageing,[3] i.e. integrating all damage done to the arterial wall until the time of measurement, in response either to well-known CV risk factors or to other CV risk factors, such as inflammation and oxidative stress. The measurement of PWV has been recommended by the 2013 European Society of Hypertension–European Society of Cardiology Guidelines for the Management of Hypertension[4] and the Sixth Joint Task Force of the European Society of Cardiology on Cardiovascular Disease Prevention[5] in order to detect arterial stiffening and reclassify patients at intermediate risk into a higher or lower CV risk. Although a large body of evidence has been published during the last decade concerning the epidemiology, pathophysiology, and pharmacology of arterial stiffness,[6] several issues are still pending, including the therapeutic possibility to reduce arterial stiffness beyond blood pressure reduction, for instance through lifestyle changes. Indeed, the relationship between arterial stiffness and chronic low-grade inflammation, that has been well established,[7] may be explained by the role of the gut microbiome, known to play a major role in inflammatory and autoimmune disease.[8]

The article by Menni *et al.*,[9] published in the present issue of the *European Heart Journal*, provides an original and important contribution with regard to the relationship between gut microbiome composition and arterial stiffness. The authors studied 617 middle-aged women enrolled in the TwinsUK registry, a national register of adult twins recruited as volunteers without selecting for any particular disease or traits.[10] They determined aortic stiffness according to gold standard measurement of carotid–femoral PWV.[11] Microbiota analysis included microbiome composition and diversity. They additionally determined circulating serum levels of specific metabolites known to be generated by the gut microbiome and to influence CV risk: phenylacetylglutamine, trimethylamine oxide (TMAO), and indole proprionate (IPA). The major finding is that arterial stiffness is inversely correlated with gut microbiome diversity, as well as with the abundance of specific microbial taxa. The mediation analysis allowed the conclusion to be reached that the effect of gut microbiome composition on PWV is only marginally mediated by C-reactive protein (CRP), the HOMA index, visceral fat, and traditional risk factors.

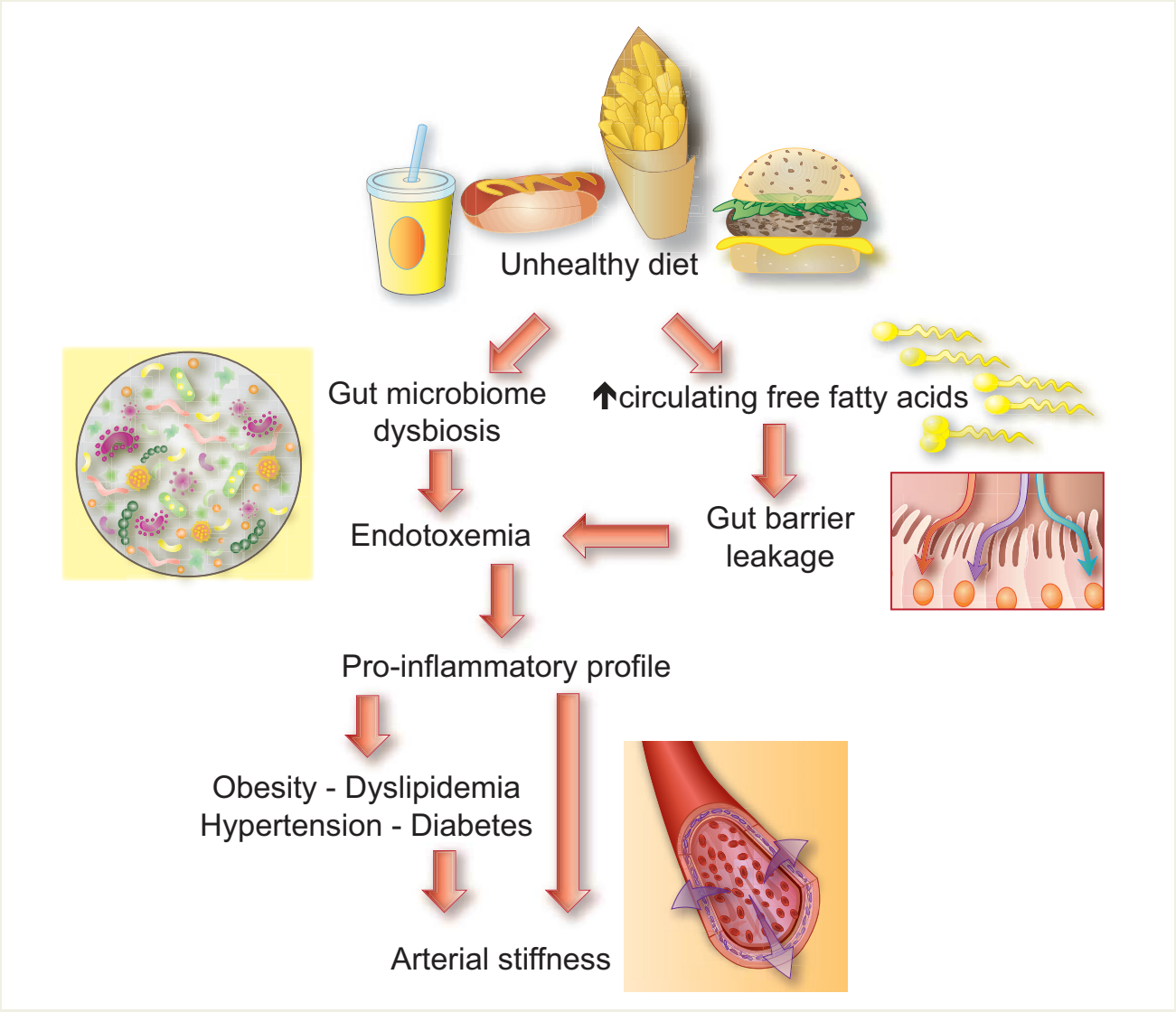
Indeed, a major strength of this study is that all analyses were adjusted for a large number of variables, including not only the three major determinants of PWV in that population [age, mean blood pressure (MBP), and body mass index (BMI)], but also other parameters known to influence PWV and seldom available in cross-sectional studies, such as dietary components and social deprivation. In particular, the relationship between PWV and the gut microbiome composition remained significant after adjustment to four categories of confounding factors: (i) lifestyle risk factors such as smoking/alcohol drinking habits, physical activity, adherence to Mediterranean diet, socio-economic status, and proton pump inhibitor (PPI) and antibiotic use; (ii) traditional cardiovascular risk factors such as the 10-year ASCVD (atherosclerotic cardiovascular disease) risk score; (iii) inflammatory markers, such as CRP; and (iv) metabolic factors, such as visceral fat mass and insulin resistance.

The findings of Menni *et al.*[9] are also stimulating because the authors state in their Introduction that arterial stiffness 'is weakly or unrelated to conventional risk factors'. Although the reader understands that this is a way to suggest that further studies should be done to detect non-CV determinants, still the major influence of age and MBP has been overlooked in this statement, since age and MBP can explain up to 50% of PWV variance in the general population according to the Reference Value Collaboration study.[12] The authors observed that microbiome factors explained 4.1–8.4% of the variance of PWV, whereas ASCVD score, HOMA index, and visceral fat taken together explained 5.51–11.24% of PWV variance. These numbers

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

† doi:10.1093/eurheartj/ehy226.

* Corresponding author. Department of Pharmacology and INSERM UMR 970, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Université Paris Descartes, 20, rue Leblanc, 75015 Paris, France. Tel: +33 1 56 09 39 91, Fax: +33 1 56 09 39 92, Email: stephane.laurent@egp.aphp.fr



Take home figure The gut microbiome and arterial stiffness: possible underlying mechanisms.

have been obtained after adjustment for age, MBP, and BMI. Unfortunately, the authors did not detail which percentage of PWV variance was explained by age, MBP, and BMI taken together. Nevertheless, it is impressive that microbiome-related variables were able to explain 4–8% of the variance of PWV, thus capturing a novel source of CV risk beyond classical risk factors, mostly unexplained from the mechanistic point of view. The authors hypothesized that chronic endotoxaemia, leading to low-grade inflammation, might be the missing link. Excess dietary fat intake seems to be the dietary component most likely to compromise gut barrier function and induce endotoxaemia.[13] A number of bacterial components are then able to activate innate and adaptive immune responses, which may trigger alterations in glucose and lipid metabolism, as well as obesity and hypertension, with a pro-atherosclerotic effect.[14] How these mechanisms might impact arterial mechanical properties regardless of classical cardiovascular risk factors should be explored in future mechanistic studies (*Take home figure*).

Although the findings of Menni *et al.*[9] have added an important piece to this puzzle, many aspects still need to be clarified. Unfortunately, no markers of endotoxaemia have been measured in this study; furthermore, CRP, included in the analysis as a marker of low-grade inflammation, impacted only marginally on the relationship between PWV and microbiome-related variables; finally, the role of dietary fats has not been explored. Other limitations of the study, which have been well discussed by the authors, include the middle-aged white female status, the delay between faecal sample collection and PWV measurement, and the cross-sectional nature of the study. In addition, a remarkable feature of the study is that it included twins. However, although family relatedness was taken into consideration for statistical adjustment, it appears that the influence of the genetic component on arterial stiffness has not been analysed by itself or through its interaction with the microbiome composition. Finally, it is important to underline that other studies did not find an association between CV-related variables, such as lifetime CV risk, and

microbiome diversity, or found associations with the abundance of different bacterial taxa. Furthermore, among microbiome-related variables, the strongest association with cardiovascular events is available for TMAO,[15] which does not seem to influence PWV in the present study.

In conclusion, the study by Menni *et al.*[9] provides a valuable contribution to the ongoing research on the relationship between arterial stiffness and inflammation. The authors demonstrated that it was possible to capture, through the characterization of the gut microbiome, a part of the CV risk that was not explained by classical risk factors. These data suggest that the gut microbiome may act as a third player in the inflammation–stiffness relationship.

Funding

This work was supported by INSERM, Assistance Publique-Hopitaux de Paris, and Paris Descartes University (S.L.), and University of Pisa, Pisa, Italy (R.M.B).

Conflict of interest: none declared.

References

1. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001;**37**:1236–1241.
2. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, Hwang SJ, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier B, Pereira T, Vasan RS, Shokawa T, Sutton-Tyrell K, Verbeke F, Wang KL, Webb DJ, Hansen TW, Zoungas S, McEniery CM, Cockcroft JR, Wilkinson IB. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 2014;**63**:636–646.
3. Nilsson P, Boutouyrie P, Laurent S. Vascular aging: a tale of EVA and ADAM in cardiovascular risk assessment and prevention. *Hypertension* 2009;**54**:3–10.
4. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, DeBacker G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;**34**:2159–2219.
5. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
6. Laurent S, Marais L, Boutouyrie P. The non-invasive assessment of vascular aging. *Can J Cardiol* 2016;**32**:669–679.
7. Zanoli L, Boutouyrie P, Fatuzzo P, Granata A, Lentini P, Ozturk K, Capello M, Theocharidou E, Tuttolomondo A, Pinto A, Camma C, Licata A, Blanco J, Rasteli S, Inserra G, Castellino P, Laurent S. Inflammation and aortic stiffness: an individual participant data meta-analysis in patients with inflammatory bowel disease. *J Am Heart Assoc* 2017;**6**:e007003.
8. Clemente JC, Manasson J, Scher JU. The role of the gut microbiome in systemic inflammatory disease. *BMJ* 2018;**360**:j5145.
9. Menni C, Lin C, Cecelja M, Mangino M, Matey-Hernandez ML, Keehn L, Mohney RP, Steves C, Spector TD, Kuo CF, Chowienczyk P, Valdes AM. Gut microbial diversity is associated with lower arterial stiffness in women. *Eur Heart J* 2018;**39**:2390–2397.
10. Moayyeri A, Hammond CJ, Valdes AM, Spector TD. Cohort Profile: TwinsUK and healthy ageing twin study. *Int J Epidemiol* 2013;**42**:76–85.
11. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;**27**:2588–2605.
12. The Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010;**31**:2338–2350.
13. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 2007;**56**:1761–1772.
14. Caesar R, Fak F, Backhed F. Effects of gut microbiota on obesity and atherosclerosis via modulation of inflammation and lipid metabolism. *J Intern Med* 2010;**268**:320–328.
15. Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, Wu Y, Hazen SL. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med* 2013;**368**:1575–1784.

Corrigendum

doi:10.1093/eurheartj/ehy115
Online publish-ahead-of-print 5 March 2018

Corrigendum to: Cardiac screening in Nepal [*Eur Heart J* (2018);39(5):339–340].

The authors of the above paper wish to inform readers that the authors' names were ordered incorrectly with the family names listed before the given names. This has now been corrected online.