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Tribute to Michel E. Safar (1937–2024): A Groundbreaker in the Concept of Hypertension

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Abstract

The authors present a short review of the personality, clinical and scientific contributions of a distinguished member of our Academy, the Artery Society and so many others, where he contributed landmark advances in many fields of arterial function and cardiovascular risk. The Editorial Board of the Artery Research Journal and the Executive Committee of the Artery Society present their due respects to Prof. Michel Safar.

Keywords Michel Safar, Hypertension, Large arteries, Central hemodynamics, Arterial stiffness

Michel Safar, Professor of medicine in Paris, passed away on 28 January 2024. Our first thoughts are with his family who mourn the loss of a husband and father figure. However, his professional family is feeling the loss of its mentor. Over the years, people have come from all corners of the world to work in his team while others from within the group have moved to every continent. All have claimed a shared identity—an essential criterion for belonging to a school—as was summarized in the book *The Paris Vascular School, 50 years pioneering research in vascular biology and medicine*, edited in 2019 by two close friends, Harry Struijker-Boudier and Moyra Barbier.

Michel Safar was born in 1937 in Algiers where his father ran a pharmacy. Although his ancestors had been based in North Africa since the sixteenth century diaspora, in 1950, the Safar family decided to leave

Algeria for Paris, where Michel Safar continued his schooling and began studying medicine.

The 4 years between 1962 and 1966 saw the recently qualified Dr Michel Safar working as a resident physician. He was initially drawn to nephrology and his first challenge in the department of his *patron*, Prof Paul Milliez, was to open a dialysis day-care centre. The intrinsic links between nephrology and hypertension sparked his initial curiosity for research. One of the first notable encounters during that period was with the nephrologist, Jean-Marie Idatte, who was to become a close friend. And a further chance encounter led him to become acquainted with Gérard London in 1968—the starting point of another long-standing friendship but also of the idea for a laboratory of clinical vascular investigation with a specific focus on hypertension.

Michel Safar published his first paper: *Arterial hypertension associated with repeated chronic hemodialysis before and after binephrectomy: hemodynamic, isotopic and biologic study*, in *J Urol Nephrol* (Paris) in 1968 [1].

In the early 1970s, the first encounter between Michel Safar, the clinical hypertension researcher, and Bernard Levy, the basic cardiovascular research scientist, forged the basis of a subsequent close collaboration between

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these two fields. While Bernard Levy was focusing on the coronary system, Windkessel and the aorta, Michel Safar was gradually turning his focus to hypertension. Patients with labile hypertension had until then been thought to have high cardiac output and therefore the main focus of assessments was cardiac blood flow. However, as he followed the work of the highly influential American physiologist Arthur Guyton, it occurred to Michel Safar that mechanical properties, and particularly the compliance of the arterial system, may have a profound influence on the more established forms of essential hypertension.

Meanwhile, following another chance meeting, Michel Safar and the mathematician Nguyen Phong Chau published a seminal paper entitled *Essential hypertension: An approach to clinical data by the use of models* [2], which integrated their clinical observations into the famous Guyton-Coleman systems analysis model of circulation. And as a premonition of another future friendship, Harry Struijker-Boudier was working as a post-doc at exactly the same time in Guyton's Mississippi Physiology Department, trying to get to grips with the Guyton-Coleman model. Michel Safar and Harry Struijker-Boudier subsequently published a series of papers on the coupling between resistances arteries and conduit arteries.

In the early 1980s, after Michael O'Rourke had reviewed one of his papers on nitroglycerin, Michel Safar and this new Australian colleague both derived great satisfaction from discussing their work. (And by a cruel twist of fate, these two colleagues and friends passed away within 8 days of each other.) Their friendship and collaboration led to several jointly written or edited important reference books, including a volume entitled *Arterial Stiffness in Hypertension* in the *Handbook of Hypertension* series (2006) [3] and a very complete, multi-authored international review book entitled *Blood Pressure and Arterial Wall Mechanics in Cardiovascular Diseases* (2014) [4].

Subsequent encounters between Michel Safar and numerous leading European and USA-based research scientists specialising in the arterial properties of hypertensive disease, and the first edition of the widely respected Paris workshops on the Structure and Function of the Vascular System in Paris, meant that, by around 1990, the requirements for the foundations of a successful school—The Paris Vascular School—had practically all been satisfied. The final prerequisite, the capacity to attract and stimulate bright young research scientists, was soon to be fulfilled.

In the 1990s, Michel Safar, and later Stephane Laurent, headed the Inserm U337 unit, created by Henri Schmitt. Although for the different generations of co-workers,

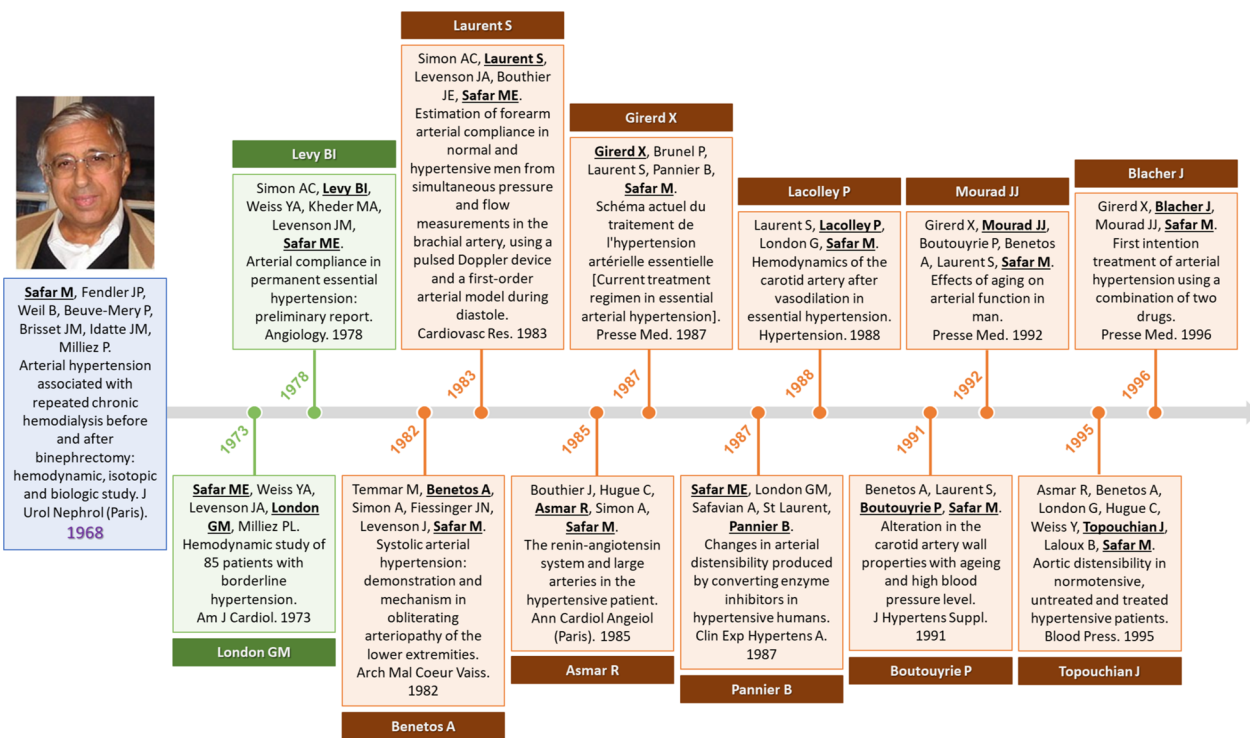


Fig. 1 First article co-authored with Michel Safar by those from the Paris Vascular School who worked alongside him or were trained by him

Michel Safar was without doubt a mentor, his humility forbade him from ever claiming such a status. Figure 1 provides an overview of many of the leading French scientists, including Bernard Levy and Gerard London, as well as the subsequent generations who worked alongside or were trained by Michel Safar. All have found their own pathway in the field of vascular research, in Paris or elsewhere, but can still be regarded as “members” of the Paris Vascular School. The publication of the textbook (*Arterial stiffness and pulsatile hemodynamics in health and disease*) [5] in 2022 and co-authored by several of his former students and graduates, is symbolic of this international influence. Despite the widespread geographic distribution, all can claim a shared identity, an essential criterion for belonging to “The Paris Vascular School”.

Michel Safar worked with several generations of doctors, biologists, nurses, engineers, and mathematicians, most of whom have gone on to have brilliant careers. All schools of thought have been encouraged, for the benefit of all concerned, and giving rise to innovative ideas and groundbreaking concepts. The ultimate proof of the success of his approach are the achievements of those whose work he fostered and the ideas that have flourished. In short, the philosophy behind “the Safar School” has always meant looking beyond what appears obvious—the very definition of

thinking outside the box—but also because his ideas rapidly became those of others.

His work has not only been instrumental in improving our understanding of the fundamental aspects of arterial stiffness but has also opened multiple new avenues in terms of clinical applications. He was a physiologist, and yet his ideas have also paved the way into physics, mathematics, psychiatry, vascular biology, and other widely different fields of research.

Michel Safar always preferred to stand back and observe how things evolved naturally, discreetly mindful of those working around him, watching how the group evolved with the essential traits of each of its members. In addition to his own publications (Table 1), he frequently chose to stay out of the limelight enabling countless seminal papers and proceedings of consensus meetings to be published with or without his co-authorship (Table 2). He worked with numerous international Societies and Organisations including ARTERY: The Association for Research into Arterial Structure and Physiology. In 2008, Michel Safar was the first to receive “The Lifetime Achievement” award from the ARTERY Society. And shortly after his death, the second edition of *Early Vascular Ageing (EVA)* was published on *New directions in Cardiovascular protection and cardiovascular translational medicine* [6]. This version was edited by P Guimarães Cunha, PM Nilsson, MH Olsen, P Boutouyrie

Table 1 Most highly cited papers by Michel Safar

Authors	Manuscript title	References
Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C [7]	Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis	Eur Heart J. 2010;31:1865–71
Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H, Wang JG, Wilkinson IB, Williams B, Vlachopoulos C [8]	Central blood pressure measurements and antihypertensive therapy: a consensus document	Hypertension. 2007;50:154–60
Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, Roman MJ, Safar ME, Segers P, Smulyan H [9]	Role of pulse pressure amplification in arterial hypertension experts' opinion and review of the data	Hypertension. 2009;54:375–83
Levy BI, Schiffrin EL, Mourad JJ, Agostini D, Vicaute E, Safar ME, Struijker-Boudier HA [10]	Impaired tissue perfusion—a pathology common to hypertension, obesity, and diabetes mellitus	Circulation. 2008;118:968–76
Protogerou AD, Safar ME, Iaria P, Safar H, Le Dudal K, Filipovsky J, Henry O, Ducimetière P, Blacher J [11]	Diastolic blood pressure and mortality in the elderly with cardiovascular disease	Hypertension. 2007;50:172–80
Safar ME [12]	Arterial stiffness as a risk factor for clinical hypertension	Nat Rev Cardiol. 2018;15:97–105
Benetos A, Thomas F, Joly L, Blacher J, Pannier B, Labat C, Salvi P, Smulyan H, Safar ME [13]	Pulse pressure amplification a mechanical biomarker of cardiovascular risk	J Am Coll Cardiol. 2010;55:1032–7
Safar ME, Asmar R, Benetos A, Blacher J, Boutouyrie P, Lacolley P, Laurent S, London G, Pannier B, Protogerou A, Regnault V; French Study group on Arterial Stiffness [14]	Interaction between hypertension and arterial stiffness: an expert reappraisal	Hypertension. 2018;72:796–805
O'Rourke MF, Safar ME, Dzau V [15]	The Cardiovascular Continuum extended: aging effects on the aorta and microvasculature	Vasc Med. 2010;15:461–8
Temmar M, Liabeuf S, Renard C, Czernichow S, Esper NE, Shahapuni I, Presne C, Makdassi R, Andrejak M, Tribouilloy C, Galan P, Safar ME, Choukroun G, Massy Z [16]	Pulse wave velocity and vascular calcification at different stages of chronic kidney disease	J Hypertens. 2010;28:163–9

Table 2 Seminal representative publications of the major areas of research

Authors	Manuscript title	References
Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI [17]	Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies	Hypertension. 1995;26:485–90
Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM [18]	Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease	Hypertension. 1998;32:570–4
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 [19]	Expert consensus document on arterial stiffness: methodological issues and clinical applications	Eur Heart J. 2006;27:2588–605
Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H, Wang JG, Wilkinson IB, Williams B, Vlachopoulos C [8]	Central blood pressure measurements and antihypertensive therapy: a consensus document	Hypertension. 2007;50:154–60
Nilsson PM, Boutouyrie P, Laurent S [20]	Vascular aging: a tale of EVA and ADAM in cardiovascular risk assessment and prevention	Hypertension. 2009;54:3–10
Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, Roman MJ, Safar ME, Segers P, Smulyan H [9]	Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data	Hypertension. 2009;54:375–83
Reference values for arterial stiffness' collaboration [21]	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;31:2338–50
Lacolley P, Regnault V, Segers P, Laurent S [22]	Vascular smooth muscle cells and arterial stiffening: relevance in development, aging, and disease	Physiol Rev. 2017;97:1555–617

and S Laurent and endorsed by the ARTERY Society, LATAM and the European Society of Hypertension, with Michel Safar's name appearing 92 times in the references.

The hallmark of all truly great scientists is their capacity to uncover new fields of research, providing conundrums, enigmas and mysteries to keep new generations of investigators busy for decades to come. Prof Michel Safar's legacy will live on as that of an outstanding scientist but also, highlighting his more personal qualities, as that of a man of culture and great humanity.

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