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Where has pathophysiology gone in the era of evidence-based medicine? In Memoriam of Giuseppe Maria Andreozzi (1945-2026)

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Professor Giuseppe Maria Andreozzi passed away on January 10, 2026.

Born on October 13, 1945, he was a distinguished Italian physician and an internationally respected researcher in the field of Vascular Medicine.

He served as Professor of Angiology at the University of Catania until 1997, after which he moved to the University of Padua, where he became Chief of the Angiology Unit.

Professor Andreozzi was a past President of the Italian Society of Angiology and Vascular Medicine (SIAPAV) and an active member of the most important international scientific societies of vascular medicine.

Throughout his career, he authored more than 400 scientific publications on Angiology.

Among these, the SURVET study stands out as a lasting reference for clinicians and researchers. This landmark work paved the way for contemporary guidelines by clearly distinguishing bleeding risk from the benefits of antithrombotic therapy in preventing recurrent deep vein thrombosis.[1]

I had the personal privilege of being his student and fellow, sharing subsequently forty years of medical practice and intellectual exchange with him. Through discussions, collaborations,

and careful reading of his work, one can unmistakably perceive his profound passion for studying the pathophysiology of vascular diseases.

In particular, Professor Andreozzi devoted much of his research in elucidating the link between inflammation and endothelial dysfunction in peripheral arterial disease, focusing on three fundamental mechanisms: i) oxidative stress, the major pathogenic driver, leading to the generation of reactive oxygen species that directly damage the endothelium;[2,3] ii) cytokines, elevated levels of pro-inflammatory mediators, such as TNF-α, IL-6, and IL-8, sustain inflammation and promote endothelial dysfunction; [3,4] iii) biomarkers, circulating markers, including C-reactive protein (CRP) and IL-6, reflect ongoing inflammation and increased vascular risk.[3-6]

Collectively, these mechanisms illustrate how inflammation induces endothelial damage and dysfunction, creating a pro-atherosclerotic environment that ultimately results in arterial stiffness and severe vascular disease.

This raises an important question: what is the place of Professor Andreozzi's teachings today? Are they still central to our understanding of vascular disease, or should they be regarded as an elegant but now repetitive exercise, rendered obsolete by the abundance of contemporary evidence?

Undoubtedly, extensive research has been conducted on the inflammation-endothelial dysfunction-atherosclerosis axis.[4] Over the past decade in particular, this topic has been explored in great depth, with major clinical and therapeutic implications, especially in vascular medicine. The evolution of knowledge regarding the role of lipids in atherogenesis and the anti-inflammatory benefits of modern lipid-lowering therapies has profoundly improved outcomes in peripheral vascular disease.[6-10]

Yet, when reading many recent clinical trials or meta-analyses, one cannot help but notice that only a few lines are often devoted to the pathophysiological interpretation of the results.

This observation inevitably leads to a broader question: where has pathophysiology gone in the era of evidence-based medicine?

The rise of evidence-based medicine and the decline of pathophysiology

The emergence of Evidence-Based Medicine (EBM) in 1992 revolutionized clinical practice by prioritizing empirical evidence derived from randomized trials and systematic reviews10. While this paradigm shift has undeniably improved patient care, it also raises concern as to whether pathophysiology - the study of disease mechanisms - has been marginalized in the process.

Traditionally, pathophysiology has represented the cornerstone of medical education and clinical reasoning, offering a deep understanding of the biological processes underlying disease.[11] It has guided diagnostic reasoning, therapeutic decisions, and preventive strategies. With the advent of EBM, however, the emphasis has increasingly shifted toward the application of population-based evidence to individual patients, sometimes at the expense of mechanistic understanding.

Neglecting pathophysiology carries several potential risks: i) over-reliance on guidelines, clinicians may apply recommendations rigidly, without sufficient consideration of individual patient characteristics or clinical nuances; ii) misdiagnosis or delayed diagnosis, insufficient understanding of disease mechanisms may lead to missed atypical presentations or rare conditions; iii) inadequate treatment, failure to appreciate the underlying pathophysiology can result in ineffective or even harmful therapeutic choices.

Should pathophysiology be reintegrated into EBM?

The answer is unequivocally yes.

Without the foundational principles of pathophysiology that I learned from Professor Andreozzi, it would be difficult to fully grasp concepts such as atherosclerotic plaque

stabilization or to understand why peripheral arterial disease is associated with the highest mortality among all manifestations of atherosclerosis.

In his studies, Andreozzi clearly demonstrated that gait-induced ischemia in untreated intermittent claudication leads to increased levels of IL-6 and CRP, accompanied by heightened systemic oxidative stress. This inflammatory *milieu* is capable of inducing plaque instability in the coronary and carotid arteries, as well as causing microcirculatory dysfunction.[4]

Following Professor Andreozzi's teachings, one can still draw important lessons for contemporary practice: i) emphasize mechanistic thinking, clinicians should be encouraged to critically analyze disease mechanisms and their relevance to individual patients; ii) use pathophysiology to interpret evidence, when applying EBM guidelines, the underlying biological mechanisms should be considered, as they may influence therapeutic decisions and outcomes; iii) foster collaboration, dialogue among basic scientists, clinicians, and policymakers should be promoted to ensure that clinical guidelines are grounded in a robust understanding of disease mechanisms.

In conclusion, what is the legacy of Professor Andreozzi?

His work reminds us that although EBM has significantly improved patient outcomes, the central role of pathophysiology in understanding disease must not be forgotten.[12] By reintegrating mechanistic insight into clinical practice, we can move toward more personalized, effective, and innovative patient care - precisely the vision that guided Professor Andreozzi throughout his distinguished career.

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