

The Arterial Biomechanics and Translational Medicine Saga

La saga de la biomecánica arterial y la medicina traslacional

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ABSTRACT

Translational medicine can be described as the interdisciplinary application of biomedical research for the improvement of health of patients and the society.

This article describes the translational medicine activities related to arterial biomechanics carried out by a group of researchers from the IMETTYB (Instituto de Medicina Traslacional, Trasplante y Bioingeniería) CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas)-Favaloro University.

Key words: Arterial biomechanics – Translational medicine - Arterial stiffness - Pulse wave velocity - Arterial thickness - Related drugs

RESUMEN

La medicina traslacional puede ser definida como la aplicación de la investigación biomédica para la recuperación de la salud, tanto de los pacientes como de la comunidad en un amplio campo interdisciplinario.

En este artículo se describe la actividad en medicina traslacional circunscripta a temas de biomecánica arterial llevada adelante por un grupo de investigadores del IMETTYB (Instituto de Medicina Traslacional, Trasplante y Bioingeniería) - Universidad Favaloro.

Palabras clave: Biomecánica arterial - Medicina traslacional - Rigidez arterial - Velocidad de onda de pulso - Espesor arterial - Fármacos relacionados

INTRODUCTION

In 1996 Dr. Alberto Agrest wrote *The Renin Saga*. (1) Renin, a chemical mediator, was discovered by Tigerstedt in the 19th century. Interestingly, it was the Finnish researcher mentioned above who developed the first quantification of arterial elasticity. (2) Renin and pulse wave velocity (PWV), a benchmark of arterial wall stiffness, are closely related to hypertension. Although it took a century for the study of PWV to be applied to large populations of hypertensive patients, it is undeniable that this step from the experimental stage to medical practice is an example of translational medicine, according to current criteria. (3)

According to Rodolfo Rey, principal researcher at CONICET and the director of CEDIE (Centro de Investigaciones Endocrinológicas “Dr. César Bergadá”), CONICET-FEI-GCABA (Fundación Endocrinológica

Infantil-Gobierno de la Ciudad Autónoma de Buenos Aires), "There are few institutions in Argentina that have traditionally conducted translational research in medicine because the groups that did basic research and those that did clinical research were distant. Very few places had both."

This article describes the translational medicine activities related to arterial biomechanics carried out by a group of researchers from the IMETTYB (Instituto de Medicina Traslacional, Trasplante y Bioingeniería) CONICET-Favaloro University.

About translational medicine

A definition accepted by the scientific community mentions that translational medicine would be the interdisciplinary application of biomedical research for the improvement of health of patients and the society. (3)

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Biomedical research at the institution of the authors of this article began as an isolated initiative that later became associated with institutions such as CONICET and INSERM (Institut National de la Santé et de la Recherche Médicale, France). Research was generated within the framework of cooperation agreements, the most notable of which are those with INSIBIO-CONICET (Instituto Superior de Investigaciones Biológicas de San Miguel de Tucumán) and the Department of Physiology at the Faculty of Medicine of the University of the Republic (Uruguay).

The original lines of research and subsequent studies covered numerous areas of biomedical knowledge. This article only mentions those related to arterial biomechanics.

The experimental stage of knowledge that was later applied in clinical practice included basic and applied research. In this regard, it is important to adhere to the definitions of the Frascati Manual. (4)

Since we are dealing with more than four decades of scientific production published at the regional level and in peer-reviewed scientific journals, we will make a synthesis considering only two main areas:

1. Indices and indicators of arterial function used in biomedical laboratory research that were later incorporated into medical practice, and
2. Experimental models in which arterial function was analyzed in a laboratory setting to characterize physiological and abnormal states.

Objectives

This article describes:

- a. General aspects of how arterial biomechanics evolved,
- b. The beginnings of experimental laboratory research,
- c. A synthesis of experimental vascular function indices, and
- d. The implementation and use of these indices in clinical cardiology.

A brief history of the beginnings of arterial mechanics

The first scientific contribution to show a variable involved in arterial mechanics was the measurement of intra-arterial pressure in an equine performed by Hales in 1733. (5) More than a century later, in 1847, Karl Ludwig plotted the temporal pressures of a canine carotid artery. (6) A significant advance occurred soon after, when Tigerstedt quantified the elasticity of the vascular wall and determined the PWV for the first time in 1893. (2) By 1933, Schretzenmayr (7) experimentally demonstrated that increases in arterial flow produced an increase in vascular diameter.

Intraluminal pressures and arterial diameters are variables used to characterize arterial mechanics. However, these contributions were not incorporated into medical practice until the second half of the 20th century. Moreover, the noninvasive blood pressure measurement technique developed by Riva Rocci in

1896 (8) did not significantly impact medical practice, despite the publication by John Welton Fisher in JAMA in 1914 demonstrating the consequences of hypertension. (9)

In 1922 Bramwell and Hill published an analysis of arterial PWV and emphasized its dependence on the elasticity of the vascular wall. (10) Then, in the second half of the 20th century, the study of arterial mechanics gained momentum when Hardung measured arterial elasticity in 1953. (11)

First Argentine contributions to arterial biomechanics

The IMETTYB includes topics that began to be developed in 1983, as the line of research "Cardiovascular Dynamics and Circulatory Support".

Since the 1980s, it has been possible to characterize the contributions of the components of the arterial wall in chronically instrumented, conscious animal models. (12-15) In this initial stage, the roles of collagen, elastin, and vascular smooth muscle could be identified in arterial pressure-diameter curves. This information can currently be found in articles included in PubMed. These investigations were conducted in an experimental laboratory in Argentina, and the data were analyzed in collaboration with French researchers from INSERM led by Dr. Alain Simon.

Based on these investigations, our goal was to analyze the contributions of each of the three layers that make up the arterial wall. For this purpose, we chose an *in vitro* model to study the arterial wall dynamics. And that is how we demonstrated for the first time that variations in hematocrit caused changes in vascular smooth muscle dynamics. (16) Next, we incorporated an anesthetized *in vivo* animal model to characterize the role of the adventitia (17). Finally, we used an *in vivo* animal model with heart failure that was treated with intra-aortic balloon pumping to demonstrate the role of the adventitia in the smooth muscle dynamics of the arteries. (18)

At this stage, the experimental research carried out at Favaloro University with a group of researchers from University of the Republic (Uruguay) analyzed the role of the endothelium in heart failure treated with intra-aortic balloon pumping. (19)

Finally, we analyzed the dynamics of the isolated media (muscular) layer (i.e., without the intima and adventitia layers) under the same conditions. (20)

Summary of indices and indicators incorporated in translational medicine

One of the criteria used to show the scientific activity in translational medicine was to compile a list of a dozen indices and indicators of arterial dynamics derived from publications in the experimental stage and reports on their implementation in medical practice (Table 1)

Since the authors are part of an interdisciplinary group and of other biomedical research associations, the bibliographic references include works with at

Table 1. Vascular indices and indicators used at different stages of the process

INDICATOR	EXPERIMENTAL STAGE	MEDICAL PRACTICE STAGE
Arterial compliance	Chau 1992 (21), Cabrera Fischer 2010 (17), Cabrera Fischer 2013 (18)	Chau 1992 (21), Christen 1997 (22), Brandani 2000 (23)
DABAC/SABAC	Cabrera Fischer 2004 (24)	Cabrera Fischer 2001 (25), Camus 2004 (26)
Arterial diameter	Cabrera Fischer 1987 (12)	Gamero 1999 (27)
Arterial distensibility	Armentano 1994 (28), Cabrera Fischer 2010 (17), Cabrera Fischer 2013 (18)	Armentano 1995 (29)
Arterial thickness	Cabrera Fischer 1988 (13)	Gamero 1999 (27)
Alx index	Wray 2021 (30)	Díaz 2018 (31)
Peterson's module	Cabrera Fischer 1991 (14), Cabrera Fischer 2005 (32), Cabrera Fischer 2009 (33)	Armentano 2006 (34)
Blood pressure	Cabrera Fischer 1987 (12), Cabrera Fischer 1988 (35)	Pessana 2021 (36), Sánchez 2020 (37), Sánchez 2022 (38)
Arterial viscosity	Barra 1997 (39)	Christen 2010 (40)
Pulse wave velocity	Armentano 1994 (28), Cabrera Fischer 2010 (17)	Christen 1997 (22), Cabrera Fischer 2009 (41), Cabrera Fischer 2018 (42)

Alx: augmentation Index; DABAC/SABAC: index that quantifies the effects of intra-aortic balloon pumping (diastolic area beneath the aortic curve/ systolic area beneath the aortic curve).

Table 2. Contributions of research to medical practice

ENTITY	EXPERIMENTAL STAGE	MEDICAL PRACTICE STAGE
Endothelium	Cabrera Fischer 2002 (16)	Christen 2010 (40)
Vascular smooth muscle	Barra 1997 (39)	Armentano 2006 (43)
HTN	Cabrera Fischer 1993 (44)	Gamero 1999 (27)
HF	Cabrera Fischer 1985 (45), Cabrera Fischer 2004 (46)	Cabrera Fischer 2001 (25)
Atherosclerosis	Cabrera Fischer 1991 (14)	Christen 2006 (47)
Renal function	Fischer P 2000 (48)	Sánchez 2007 (49)
ANS control	Risk 2004 (50)	Ramírez 2003 (51)
ACEI	44-Cabrera Fischer 1993 (44), Barra 1997 (39)	Ramírez 2019 (52)
Beta blockers	Crottogini 1987 (53)	Armentano 2001 (54)
Calcium channel blockers	Crottogini 1985 (55)	Ramírez 2019 (56)

Clinical situations of normality, disease and therapeutics that ventured from the experimental stage at the biomedical laboratory to medical practice.

ACEI: angiotensin-converting enzyme inhibitor. ANS: autonomic nervous system; HF: heart failure; HTN: hypertension.

least one author from the institution. On the other hand, it should be noted that not all indices or indicators of arterial function have been included, as the quantification of atherosclerotic plaque by fractal dimension analysis.

Table 1 includes the controversial blood pressure augmentation index (AIx), which has been analyzed experimentally since 2008 as part of a scientific and technological research project funded by the National Ministry of Science and Technology. Due to the lack of convincing evidence regarding the sensitivity and specificity of AIx, the decision was made to submit two manuscripts summarizing the experimental and clinical analyses.

Summary of the contributions of medical practice to translational medicine

Table 2 lists the clinical conditions (normal and abnormal) that were analyzed in the experimental laboratory and in medical practice, in parallel to the reported uses of indices and indicators of function and structures related to vascular biomechanics. Table 2 includes the treatments used in patients with specific conditions for which biomechanical analysis is performed or is under development.

Considerations on translational medicine in arterial biomechanics

The study of cardiovascular pathophysiology in the experimental laboratory is supported by animal models that replicate those published in the specialized literature. When there is a gap in the literature, new models are developed, such as those published by the authors. (45,18) This does not mean that experimental laboratory developments will always be transferred to medical practice. For example, the numerous works on adventitial function carried out by the IMETTYB group are not cited because they have not ventured into the field of patients. This fact underscores the wealth of knowledge generated by the laboratory and the underutilization of this knowledge in medical practice.

Just as the study of left ventricular function analyzes the dynamics of the ventricular wall, arterial mechanics focuses on the vascular walls. In both structures, mechanical analysis provides functional indices of significant diagnostic value. However, the study of arterial biomechanics has been recently introduced. This underscores the importance of using and analyzing new vascular function indices in different experimental models of various conditions.

In summary, the objectives of this article have been developed using part of the analyses that have been carried out and published over a period of four decades.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material).

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