Models of Human Vascular Disease: Is There an Animal of La Mancha?

The MIT Faculty has made this article openly available. Please share how this access benefits you. Your story matters.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Balcells, Mercedes, and Edelman, Elazer R. “Models of Human Vascular Disease: Is There an Animal of La Mancha?” Revista Española de Cardiología (English Edition) 64, 9 (September 2011): 739–742</th>
</tr>
</thead>
<tbody>
<tr>
<td>As Published</td>
<td><a href="http://dx.doi.org/10.1016/j.rec.2011.05.014">http://dx.doi.org/10.1016/j.rec.2011.05.014</a></td>
</tr>
<tr>
<td>Publisher</td>
<td>Elsevier</td>
</tr>
<tr>
<td>Version</td>
<td>Author's final manuscript</td>
</tr>
<tr>
<td>Accessed</td>
<td>Sat Dec 08 10:12:36 EST 2018</td>
</tr>
<tr>
<td>Citable Link</td>
<td><a href="http://hdl.handle.net/1721.1/112782">http://hdl.handle.net/1721.1/112782</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>Creative Commons Attribution-Noncommercial-Share Alike</td>
</tr>
<tr>
<td>Detailed Terms</td>
<td><a href="http://creativecommons.org/licenses/by-nc-sa/4.0/">http://creativecommons.org/licenses/by-nc-sa/4.0/</a></td>
</tr>
</tbody>
</table>
Models of Human Vascular Disease: Is There an Animal of La Mancha?

Modelos de la enfermedad vascular humana: ¿hay un animal de La Mancha?

Mercedes Balcells\textsuperscript{a,b,}\textsuperscript{*} and Elazer R. Edelman\textsuperscript{a,c}

\textsuperscript{a}Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States
\textsuperscript{b}Institut Químic de Sarrià, Universitat Ramon Llull, Barcelona, Spain
\textsuperscript{c}Cardiovascular Division, Brigham and Women’s Hospital, Boston, Massachusetts, United States

"Les han de traer ejemplos palpables, fáciles, inteligibles, demostrativos, indubitables, con demostraciones matemáticas que no se pueden negar"

\textit{(El Ingenioso Hidalgo Don Quijote de la Mancha, 1, XXXIII)}

(Translation: They need examples that are tangible, easy, understandable, illustrative, indubitable, and with mathematical proofs that cannot be denied).

Cervantes understood that models—be they physical or moral lessons—are valid only in as much as they mirror that which they seek to mimic. This is the essential issue presented by Diego et al.\textsuperscript{1} in the article published in \textit{Revista Española de Cardiología}. Drug-eluting stents have changed the practice of medicine and are perhaps the most common intervention used today. Millions of stents are placed each year and yet critical questions remain as to whether one design is better than another. The challenge in major part is that, though device designs may be significantly different one from another, detection of a clinical difference is difficult given the rarity of side effects. Human clinical trials are too small and too short to detect differences even in fatal events that occur in 1 in 100 patients per year. The natural fallback is to rely on animal model systems and yet it is unclear how best to use them. Diego et al.\textsuperscript{1} describe a study that compares the proliferative response elicited after deployment of paclitaxel-eluting and bare metal stents in porcine coronary arteries. They suggest that the ability of a stent platform to significantly impact late vascular healing depends upon the degree of injury that is created at the time of implantation. Such a result has profound impact on how we consider animal model systems for critical technologies, our view of vascular biology and vascular repair, and our appreciation of the history of work in this field. Moreover, the study shows how a difficult parameter rarely controlled in human interventions—the extent of injury—is such a powerful regulator of clinical effect and restenotic side effect.

\textsuperscript{*}Corresponding author: Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, 77 Massachusetts Avenue, E25-438, Cambridge, MA 02139, United States. merche@MIT.EDU (M. Balcells).

CONFLICTS OF INTEREST

None declared.
Angioplasty came to clinical fruition in 1979 with the pioneering work of Gruntzig et al.\textsuperscript{2} and endovascular stenting in the late 1980s as the result of equally heroic efforts by Palmaz et al.\textsuperscript{3} and Gianturco et al.\textsuperscript{4} In a fascinating way clinical impact was realized early but required development of precise preclinical model systems\textsuperscript{5–8} before full clinical potential could be realized, and detailed aspects of safety required more complete understanding of the basic biology. It is the latter which is the most recent addition to the biology of stents and the elements of stent biology that rely most on historical contributions. Indeed, Santiago Ramón y Cajal early in his career proposed what was then a controversial issue: the origin of inflammation and the migration of leukocytes, and worked later in understanding the morphology and anatomy of endothelial cells and their interaction with leukocytes.\textsuperscript{9} Yet, it took almost 75 years for the role of inflammation in vascular disease to come front and center—in major part because it was difficult to measure inflammation in man and there were few accurate animal models of inflammation and vascular disease. In 1908 Ignatowski\textsuperscript{10} produced the first animal model of atherosclerotic disease by feeding rabbits a special diet rich in meat, milk, and eggs. Many models followed and in the late 1970s Vesselinovitch\textsuperscript{11} listed an extensive wish list of the desirable features of animal models of atherosclerosis: “\textit{must be easily available and inexpensive} […] \textit{develop typical lesions with relative ease in a practical length of time}, […] \textit{have some similarity to human anatomy, physiology, and biochemistry including serum lipoprotein and lipid metabolism similar to humans}, […] \textit{and demonstrating clinical complications of lesion rupture similar to those seen in humans}.” The search for appropriate animal models to understand and treat coronary artery disease has led to high-fat diet feeding, alone or in combination with physical, chemical, and/or immunologic injury to the endothelium. There always seem to be some characteristics of the induced disease in these animal models that diverge from the naturally occurring disease in human patients and some kind of compromise needs always to be made when selecting an animal model. The objective is to establish the best possible match between the model and the specific hypothesis being tested.

With the birth of interventional cardiology and the massive adoption of stents for the treatment of atherosclerotic vascular disease, proliferative processes like intimal hyperplasia lead to restenosis, a clinically relevant event as profound as the obstructive atheromatous plaque itself. The deployment of a balloon within a semi-occluded artery reopens the artery but is accompanied by extensive recoil, endothelial cell denudation, tissue ingrowth and vessel remodeling. Stents significantly reduce recoil, and local drug elution virtually eliminates tissue overgrowth, but the device and its drug may exacerbate endothelial damage and subsequent thrombosis. What then is the correct model to use and the parameters to consider for the complex multilaminate structures that are vessels and whose disease involves architectural disruption through endothelial denudation, leukocyte adhesion, transmigration and transformation, lipid insudation, and local destruction? What aspects of vascular repair are then most important and perhaps best predictors of human safety? When and where do we look in animal model systems?

Diego et al.\textsuperscript{1} extended the questions even further by showing that late impact is heavily influenced by initial conditions. They showed that the degree of injury provoked by the device deployment dictates the proliferative response and the vascular response to specific
In light of their findings, they pose a very interesting question “Are current experimental models valid for drug-eluting stents analysis?” Animal models have been indeed very useful in elucidating the pathobiology and complex processes of atherosclerosis as well as to assess toxicity of a device, but their use to predict efficacy of stents remains limited. We ought to step back and look at the problem from different angles, going back to Ramon y Cajal’s early definitions of endothelial cells and inflammatory cells.

In truth there is likely no animal model of any human disease. It is impossible that any animal rodent or quadripedal larger species could mimic the processes that beset humans late in life. Vascular disease in the animal cannot likely ever fully reflect the cumulative sum effects of exposure to environmental factors like tobacco abuse, decades of hypertension, abnormalities in lipid and glucose metabolism, and the passing down of specific genetic defects. Animal models are invaluable, as is evident here, in addressing circumscribed questions where a specific mechanism is at play–does for example, deep vascular injury impose a different set of constraints on vascular repair than superficial injury? Here animal models are not only appropriate and relevant, but likely the only way to address this issue. The spectrum and heterogeneity of human disease cannot allow for such a question to be answered in clinical trials. Indeed, the heterogeneity of lesions within the same person confounds the premise of a single model use.

The composition and the distribution of cellular and extracellular matrix components of the tissue upon vascular intervention and drug-eluting stent implantation evolves with time and differs significantly from the original pre-implantation scenario. Recently published data demonstrate that disease-induced changes in the distribution of drug-binding proteins and interstitial lipid alter the distribution of these drugs, forcing one to consider how disease might affect the evaluation and efficacy of the local release of these and like compounds (Fig. 1). There are therefore not only spectrums of cells within the diseased artery but for each cell a range of states the cells can attain. Smooth muscle cells can exist in a synthetic or proliferative phenotype, aligned with or separated from their overlying endothelium, packed in tight array or dispersed haphazardly within collagen-rich matrix. Inflammatory cells similarly play a diverse set of roles. Monocytes are recruited by activated endothelial cells to vascular lesions. Stenting enhances these recruiting signals and brings in polymorphonuclear cells as well. Each of these cells can promote or retard healing or injury. Monocytes for example can exacerbate endothelial injury or promote endothelial cell proliferation–all depending on their state. The endothelium regulates vessel homeostasis in a density-dependent, flow-dependent, frequency of flow-dependent fashion. Ramón y Cajal knew this and we should not be surprised that changes to the structural flatness of healthy endothelial cells may be compromised by the disease environment. In short, lesions not only differ from species to species and man to man, but within every person–it is no wonder that we cannot model such events in an animal.

What then can be done? As above, we can ask good questions and appreciate interesting results as Diego el al. have done. We can also realize that while no one model can provide precise recapitulation of the human experience we can obtain deep insight through the integration of results from multiple models. We need not only focus on the biology of isolated cells on a cell culture plate or on the results obtained in a particular animal model.
Computational models will become even more powerful tools to simulate the fluid mechanic environment and to predict drug distribution along the vessel and device outcome in a patient/device specific manner.\textsuperscript{14} We have already seen sophisticated in vitro bioreactors that recapitulate not only both the cellular and matrix components but also the mechanic environments that blood vessels are exposed to.\textsuperscript{15} Clinically relevant data can only be obtained by interconnecting disciplines to develop new powerful methods. It is increasingly evident that critical clinical problems and complex cell-tissue-device interactions may be unraveled best by a pandisciplinary approach that brings engineers of all kinds and mathematicians together with biologists and physicians (Fig. 2). Only integrated approaches--computational, \textit{in vitro} and \textit{in vivo}--will enable us to bridge the gap between scientific findings and clinical applications. This is perhaps what we should learn from Cervantes. First, we need to bring “examples that are tangible, easy, understandable, illustrative…” and then support this “…with mathematical validation so that they cannot be denied”. It seems like we knew what to do a long time ago.

**ACKNOWLEDGEMENTS**

The authors thank Elsevier for permission to use materials from the original paper by Tzafriri et al.\textsuperscript{12}

**FUNDING**

Dr. Edelman’s work is funded by NIH/NIGMS RO1/GM049039 and Dr. Balcells is supported by Spain’s Ministerio de Innovación (Plan Nacional BFU2009-09804), the Barcelona Chamber of Commerce, and Fundació Empreses Institut Químic de Sarrià.

**REFERENCES**


Figure 1.
Local paclitaxel deposition scales associated inversely with lipid content in control (injury + normal diet, \( n = 2 \)) and diseased arteries (injury + cholesterol/oil diet + normal diet, \( n = 2 \)).
Fluorescent paclitaxel (green) and lipid (insert, red) distribution in control artery (a) and in lesions of varying complexity (b–d). All samples imaged at the same intensity level and processed to eliminate backgrounds and artifacts with minimal residual autofluorescence exhibited by control arteries that were incubated in phosphate saline.
Reproduced from Tzafriri et al.\textsuperscript{12} with permission from the publisher. A, adventitia; M, media; NI, neointima.
Figure 2.
The solution of a clinical problem requires pandisciplinary approaches and communication to see the problem as a whole. In parallel, we need to formulate specific questions and answer them from different angles applying a variety of methods. Application of such approaches will help us to translate clinical symptoms of complex diseases into biological targets and therapies that are patient-specific.