David Garcia-Dorado: a true pioneer in cardiac ischaemia/reperfusion injury

CVR Onlife

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Researchers in the field of cardiac ischaemia and reperfusion injury over the past 30 years will be very familiar with the name David Garcia-Dorado. Not only because of his tireless efforts as co-Editor-in-Chief (with Hans Michael Piper) of this journal, but due to his outstanding contributions to research and the cardiovascular research community. Together with Michael Piper, David spent 10 years at the helm of Cardiovascular Research, during a period of rapid change in the publication process. Meanwhile, he managed to continue a highly active research programme, publishing in total over 400 research articles, reviews and letters throughout his career. Here, we would like to highlight some of David's key research contributions to the field of cardiac ischaemia and reperfusion (IR) injury, while of course also recognizing an excellent team of fellow researchers (not least, those of the Cardiology Department of which he was head, at Vall d'Hebron University Hospital, Universitat Autonoma de Barcelona, Spain) and collaborators who have contributed to the research we describe below.

Throughout his career, David retained a keen interest in what are understood to be the key mediators of cardiac IR injury, particularly calcium and ROS. Even while popular attention moved towards calcium contained within mitochondria and its significance in stimulating opening of the mitochondrial permeability transition pore (mPTP), David never forgot the major damaging effects that calcium overload also has in the cytosol.[1] His major contributions include understanding the role of calcium in calpain-mediated proteolysis and sarcoplasmic reticulum (SR)-driven oscillations, and how this can induce hypercontracture of cardiomyocytes (Figure 1). He led the field in understanding how the Na^+/Ca^{2+} exchanger acting in the reverse mode results in cytosolic calcium overload, and how inhibition of the reverse mode action can be cardioprotective.[2]

He identified the calcium-dependent protease calpain as a major pharmacological target in ischaemia and reperfusion injury.[3, 4]. His group were the first to demonstrate that delayed long-term calpain inhibition using SNJ-1945 attenuates adverse post-infarction remodelling. Acute treatment reduced infarct size in hearts reperfused for 24 h and inflammation measured after 3 days. Oral treatment commencing 24 h after reperfusion attenuated inflammation, cardiomyocyte hypertrophy and collagen infiltration after 21 d.[5]

David was convinced that calcium-induced hypercontracture plays a key role in cardiomyocyte death during IR, and employed an ingenious range of techniques to investigate this hypothesis, both in primary cardiomyocytes and intact hearts. His pioneering study on this concept demonstrated that pharmacological inhibition of the contractile apparatus during the first minutes of reperfusion was

able to reduce infarct size in the *in situ* pig heart model[6] (cited over 120 times). Almost simultaneously, the observation of the compact geometry of reperfused infarcts was the key for a series of landmark studies on the role of cell-to-cell interaction for the wave-progression of damage during myocardial reperfusion. Using end-to-end connected isolated cardiomyocytes he demonstrated that the induction of hypercontracture in one cell was followed by hypercontracture of the adjacent cell by a gap junction-mediated passage of Na^+ and subsequent calcium overload.[7] This research led him to perform a study, published in Circulation, showing that the *in vivo* administration of the gap junction uncoupler heptanol during reperfusion prevented cell-to-cell progression of hypercontracture and reduced infarct size.[8] Moreover, and contrary to the prevailing concept, David's studies demonstrated that gap junctions remain open during the initial stage of ischemia, favouring the transmission of ischemic rigor contracture and contributing to energy exhaustion in a cell-to-cell dependent manner.[9] He also proposed that hypercontracture was involved in the mechanism of ischaemic preconditioning.[10] As a consequence of his editorial activity, perhaps, he was keenly aware of current literature and always tried to understand how his observations fitted into current understanding. For example, he showed that mPTP opening and hypercontracture were two interrelated phenomena during reperfusion, as mitochondrial calcium release upon mPTP opening aggravates cytosolic calcium overload,[11] whereas cytosolic calcium oscillations favour mPTP opening.[12] David strongly resisted the idea that apoptosis is important in acute IR injury and generated important data to convincingly support his position.[13]

Ultimately, David's main concern was for the successful treatment of the cardiac patient. Consequently, a major aim of his research was to identify approaches that could be used to protect the hearts of patients undergoing IR injury during STEMI. While the evidence for the importance of gap junctions and hypercontracture in IR injury was convincing, the question remained of how gap junctions could be pharmacologically targeted using drugs that could be utilized clinically. By pursuing his interest in intracellular communication, David arrived at connexins, which are central components of gap junctions, and specifically connexin-43. Two of his highly cited reviews from this time examine the modulatory effects of connexin-43 on cell death/survival beyond cell coupling,[14] and its potential role in the mitochondria.[15]

This research into regulators of gap junction closure led him to the interesting concept that cyclic GMP (cGMP) and protein kinase G (PKG) signalling might be an alternative pathway mediating cardioprotection separately from, or importantly, additively with, the main kinases of so-called reperfusion injury salvage kinase (RISK) pathway. Indeed, he showed that the cGMP/PKG pathway mediates myocardial postconditioning protection in rat hearts by delaying normalization of intracellular acidosis during reperfusion.[16] He thus saw the cGMP/PKG pathway as a common mediator of cardioprotection modulating the rate of recovery of intracellular pH, but also having a direct effect on Ca^{2+} oscillations and mitochondrial permeability transition.[17] He is well known for his excellent contributions in mitochondrial research, which include important studies on mitochondrial ROS and mitochondrial connexin-43.[15, 18] Recently, he performed the first experiments demonstrating that malonate prevents mPTP opening and is effective at limiting reperfusion injury in large animals.[19, 20]

David was a true clinician scientist, and successfully navigated the choppy waters flowing between basic, translational and clinical research. He was equally comfortable with research spanning from the level of intracellular organelles (SR and mitochondria) and cells to whole organisms (rodent and pig models) and patient studies. He was a strong proponent of a rigorous process for translational research, in which clinical studies are initiated only after protocols have been optimized and tested in robust pre-clinical trials and in multicentre pre-clinical randomized trials.[21] David led the field in developing the approach of multi-target therapy for cardioprotection.[22] He was the first to show in a large animal model that combination therapy using two complementary approaches (remote

ischaemic conditioning combined with either insulin or exenatide) enhances infarct size limitation.[23] Regrettably, he was not able to attend the recent ESC congress in Paris, where the results of the COMBAT-MI trial were presented. Although the outcome of this trial combining RIPC with exenatide was neutral, this might suggest that the focus of the cardioprotection field on kinases has been too narrow, and furthermore may vindicate David's focus on the inhibition of injurious mechanical processes such as calcium overload, calpain protease activity and hypercontracture.

David also played an important role in advocacy, emphasizing the importance of increasing public funding to develop cardiac therapies that may benefit patients, even if there is limited prospect for economic reward. He saw the failure to increase cardiovascular R&D funding in European Union countries that have low funding levels as "a terrible error that can be dramatically aggravated by cuts in public health expenditure".[24] Furthermore, he went on to state, "Cardiovascular scientists and cardiologists should commit themselves to combat and correct these errors which may have severe health and economic costs".

As can be seen from this brief summary, David made numerous, important and long-lasting contributions to research in the field of ischaemia and reperfusion. He inspired a great many students and researchers whom he helped to navigate the ebb and flow of research tides, while making many friends along the way. While his contributions to research will no doubt persist, he will be sorely missed.

Figure legends

Figure 1

The main mechanisms and consequences of altered Ca^{2+} handling in cardiomyocytes during initial reperfusion, which formed a focus of David's interest. Two cardiomyocytes are show to illustrate how ionic disturbances may be transmitted through gap junctions. NHE = Na^+/H^+ exchanger; NCX = Na^+/Ca^{2+} exchanger. Na^+/K^+ = Na^+/K^+ ATPase; ROS = reactive oxygen species; SR = Sarcoplasmic reticulum.

Figure 2

A moment soon to come: The old crew left ashore while the flagship journal sails out to the high seas under new command. Back row from left: H. Michael Piper, Editor-in-Chief; Elizabeth A. Martinson, Managing Editor; Associate Editors Javier Inserte, Antonia Sambola, Marisol Ruíz-Meana, José Antonio Barrabés, and Gerhild Euler; Editorial Assistant Judith Lehnhardt. Front row from left: Thomas Noll, Associate Editor; Giuliana Ríos-Quiñones, Editorial Assistant; Klaus-Dieter Schlüter, Associate Editor; David Garcia-Dorado, Co-Editor. Not shown: Associate Editors Heinrich Sauer and Rainer Schulz; Editorial Assistants Anette Gralla and Jasmine Gaspar Dörr. (Original caption, reprinted from Reprinted with permission from Cardiovascular Research, Volume 96, Issue 3, 1 December 2012, Pages 341–342.)

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Figure 1

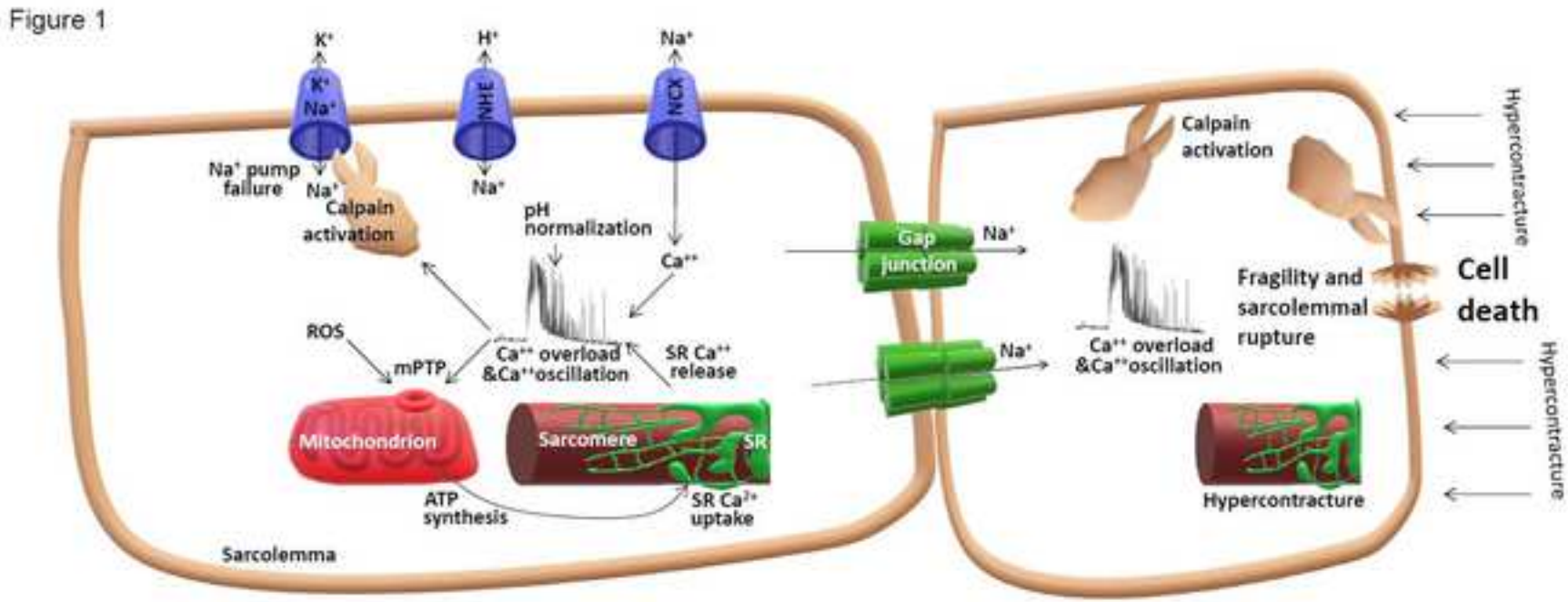

Figure 2

Figure 1 A moment soon to come: The old crew left ashore while the flagship journal sails out to the high seas under new command. Back row from left: H. Michael Piper, Editor-in-Chief; Elizabeth A. Martinson, Managing Editor; Associate Editors Javier Inserte, Antonia Sambola, Marisol Ruíz-Meana, José Antonio Barrabés, and Gerhild Euler; Editorial Assistant Judith Lehnhardt. Front row from left: Thomas Noll, Associate Editor; Giuliana Ríos-Quiñones, Editorial Assistant; Klaus-Dieter Schlüter, Associate Editor; David Garcia-Dorado, Co-Editor. Not shown: Associate Editors Heinrich Sauer and Rainer Schulz; Editorial Assistants Anette Gralla and Jasmine Gaspar Dörr.

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