Response to Letter Regarding Article, "Upregulation of $K_{2P}3.1$ K^+ Current Causes Action Potential Shortening in Patients With Chronic Atrial Fibrillation"

We thank Dr Olschewski and colleagues for their interest in our article,[1] and we appreciate their recapitulation of 2 key findings of our work: (1) the identification of increased atrial $K_{2P}3.1$ (TASK-1) K^+ channel expression, $I_{K2P3.1}$ upregulation, and action potential shortening as substrate in patients with chronic atrial fibrillation (AF); and (2) the presentation of $K_{2P}3.1$ current inhibition and resulting action potential prolongation as mechanism-based therapeutic paradigm in this subentity of the arrhythmia. Our study focused on the mechanistic contribution of $K_{2P}3.1$ channels to human atrial electrophysiology and action potential regulation, with particular emphasis on pathophysiological dysregulation in AF. Based on mechanistic data presented in the study, functional correction of atrial ionic remodeling through the suppression of atrial $K_{2P}3.1$ current emerged as a novel antiarrhythmic option for AF management.

We agree with Olschewski et al that efficacy and safety require in-depth preclinical evaluation before transfer of novel therapeutic principles into human application. In their letter, the authors highlight their findings of $K_{2P}3.1$ expression and functional significance in human pulmonary artery smooth muscle cells,[2] corresponding to previous observations by our group.[3] $K_{2P}3.1$ current in human pulmonary artery smooth muscle cells regulates vascular tone and pulmonary arterial pressure, and $I_{K2P3.1}$ reduction by endothelin-1 or genetic mutations has been implicated in the pathophysiology of pulmonary arterial hypertension. To date, clinical data on in vivo application of specific $K_{2P}3.1$ inhibitors in humans or large animals have not been reported. Thus, conclusions regarding the true extent and causal relations between systemic $K_{2P}3.1$ blockade and potential effects on pulmonary vasculature are limited. Nonetheless, pulmonary vascular tone should be carefully considered in future studies addressing $K_{2P}3.1$ as antiarrhythmic target. Similarly, caution is required regarding potential cardiac effects when direct or indirect pharmacological $K_{2P}3.1$ activation is explored as therapeutic principle in the treatment of pulmonary arterial hypertension. Increased $K_{2P}3.1$ current amplitudes may result in atrial arrhythmia including AF, associated with further worsening of symptoms and prognosis.

Gene therapy with greater selectivity than small molecule-based approaches may be used to exclude potential extracardiac side effects. The gene of interest is packaged into viral or nonviral carriers and delivered to the target area by means of direct injection or by use of catheter-based interventional techniques, providing the advantage of site-restricted action in contrast to systemic application of drugs. Previous studies confirmed effective use of gene therapeutic approaches targeting electric or structural substrates for rhythm control in large-animal models of AF.[4,5] Similarly, a better understanding of tissue-specific $K_{2P}3.1$ channel regulation and of the molecular mechanisms underlying $K_{2P}3.1$ upregulation might help to identify pathways to target increased atrial $I_{K2P3.1}$ without affecting channels in human pulmonary artery smooth muscle cells.

In summary, $K_{2P}3.1$ K^+ channels are important for determining the action potential duration in human atrial myocytes,[1] and they set the resting membrane potential and vascular tone in human pulmonary artery smooth muscle cells.[2,3] Further therapeutic exploitation of these significant mechanistic findings in cardiovascular medicine requires consideration of the potential side effects that may be minimized by the choice of application mode, appropriate dose titration, thorough preclinical evaluation, and patient monitoring.

Acknowledgments

This study was supported in part by research grants from the DZHK (Deutsches Zentrum für Herz-Kreislauf-Forschung – German Centre for Cardiovascular Research) and from the BMBF (German Ministry of Education and Research) (to C.S., F.W., X.B.Z., S.L., M.B., P.A.S., H.A.K., and D.T.)

Disclosures

The experimental compound A293 was kindly provided by Sanofi-Aventis (Frankfurt am Main, Germany). Dr Thomas served on advisory boards for and received honoraria for lectures from Sanofi-Aventis. The other authors report no conflicts.

Constanze Schmidt, MD
Felix Wiedmann, MD
Department of Cardiology
University of Heidelberg
Heidelberg, Germany

Niels Voigt, MD
Institute of Pharmacology
West German Heart and Vascular Center
University Duisburg-Essen
Essen, Germany

Xiao-Bo Zhou, MD
First Department of Medicine
University Medical Center Mannheim
Mannheim, Germany

Jordi Heijman, PhD
Department of Cardiology
Cardiovascular Research Institute Maastricht
Maastricht University Medical Centre
Maastricht, The Netherlands

Siegfried Lang, PhD
First Department of Medicine
University Medical Center Mannheim
Mannheim, Germany

Virginia Albert, BSc
Department of Cardiology
University of Heidelberg
Heidelberg, Germany

Stefan Kallenberger, MD, PhD
Department for Bioinformatics and Functional Genomics
Division of Theoretical Bioinformatics
German Cancer Research Center (DKFZ)
Institute for Pharmacy and Molecular Biotechnology (IPMB) and BioQuant
Heidelberg University
Heidelberg, Germany

Arjang Ruhparwar, MD
Gábor Szabó, MD, PhD
Klaus Kallenbach, MD
Matthias Karck, MD
Department of Cardiac Surgery
University Hospital Heidelberg
Heidelberg, Germany

(*Circulation*. 2016;133:e440-e441. DOI: 10.1161/CIRCULATIONAHA.115.020662.)

Martin Borggrefe, MD
First Department of Medicine
University Medical Center Mannheim
Mannheim, Germany

Peter Biliczki, MD, PhD
Department of Cardiology
Internal Medicine III
Goethe University
Frankfurt, Germany

Joachim R. Ehrlich, MD
Department of Cardiology
St. Josefs-Hospital
Wiesbaden, Germany

István Baczkó, MD, PhD
Department of Pharmacology and Pharmacotherapy
Faculty of Medicine
University of Szeged
Szeged, Hungary

Patrick Lugenbiel, MD
Patrick A. Schweizer, MD
Department of Cardiology
University of Heidelberg
Heidelberg, Germany

Birgit C. Donner, MD, PhD
Department of Cardiology
University of Basel Children`s Hospital
Basel, Switzerland

Hugo A. Katus, MD, PhD
Department of Cardiology
University of Heidelberg
Heidelberg, Germany

Dobromir Dobrev, MD
Institute of Pharmacology
West German Heart and Vascular Center
University Duisburg-Essen
Essen, Germany

Dierk Thomas, MD
Department of Cardiology
University of Heidelberg
Heidelberg, Germany

References

1. Schmidt C, Wiedmann F, Voigt N, Zhou XB, Heijman J, Lang S, Albert V, Kallenberger S, Ruhparwar A, Szabó G, Kallenbach K, Karck M, Borggrefe M, Biliczki P, Ehrlich JR, Baczkó I, Lugenbiel P, Schweizer PA, Donner BC, Katus HA, Dobrev D, Thomas D. Upregulation of K(2P)3.1 K+ current causes action potential shortening in patients with chronic atrial fibrillation. *Circulation*. 2015;132:82–92. doi: 10.1161/CIRCULATIONAHA.114.012657.
2. Olschewski A, Li Y, Tang B, Hanze J, Eul B, Bohle RM, Wilhelm J, Morty RE, Brau ME, Weir EK, Kwapiszewska G, Klepetko W, Seeger W, Olschewski H. Impact of TASK-1 in human pulmonary artery smooth muscle cells. *Circ Res*. 2006;98:1072–1080. doi: 10.1161/01.RES.0000219677.12988.e9.
3. Seyler C, Duthil-Straub E, Zitron E, Gierten J, Scholz EP, Fink RH, Karle CA, Becker R, Katus HA, Thomas D. TASK1 (K(2P)3.1) K(+) channel inhibition by endothelin-1 is mediated through Rho kinase-dependent phosphorylation. *Br J Pharmacol*. 2012;165:1467–1475. doi: 10.1111/j.1476-5381.2011.01626.x.
4. Bikou O, Thomas D, Trappe K, Lugenbiel P, Kelemen K, Koch M, Soucek R, Voss F, Becker R, Katus HA, Bauer A. Connexin 43 gene therapy prevents persistent atrial fibrillation in a porcine model. *Cardiovasc Res*. 2011;92:218–225. doi: 10.1093/cvr/cvr209.
5. Trappe K, Thomas D, Bikou O, Kelemen K, Lugenbiel P, Voss F, Becker R, Katus HA, Bauer A. Suppression of persistent atrial fibrillation by genetic knockdown of caspase 3: a pre-clinical pilot study. *Eur Heart J*. 2013;34:147–157. doi: 10.1093/eurheartj/ehr269.