

# Institute of Cellular and Molecular Physiology

## Professorship of Cardiovascular Physiology

### Address

Waldstraße 6  
91054 Erlangen  
Phone: +49 9131 8522301  
Fax: +49 9131 8522770  
www.physiologie2.fau.de

### Head of Division

Prof. Dr. med. Tilmann Volk

### Contact

Prof. Dr. med. Tilmann Volk  
Phone: +49 9131 8522301  
Fax: +49 9131 8522770  
physiologie2-sekretariat@fau.de

### Research focus

- Cardiac ion channels
- Electromechanical coupling

### Structure of the Professorship

Professorship: 1  
Personnel: 5  
• Scientists: 3  
(thereof funded externally: 1)  
• Graduate students: 2

### Special structural feature

The Institute of Cellular and Molecular Physiology comprises the Chair of Physiology (Systems Physiology) and the Professorship of Cardiovascular Physiology. The Chair and the Professor of Cardiovascular Physiology serve as director and deputy director of the Institute, respectively.

### Research

The research focus of the Professorship of Cardiovascular Physiology is the study of the pathophysiology of cardiac arrhythmia and heart failure. Heart failure leads to functional and structural alterations at the macroscopic as well as the microscopic and the molecular level, a process called remodeling. Cardiac remodeling during heart failure alters the electromechanical function of the heart, for example by altering the expression of ion channels that control cardiac excitation and repolarization, which increases the risk for cardiac arrhythmia including sudden death. Structural alterations in heart failure, such as an increase in connective tissue (fibrosis) or an alteration of the myocyte architecture, can decrease cardiac contractility and worsen heart failure. Our primary goal is to further understand the molecular mechanisms that underlie remodeling of the heart. This might lead to new diagnostic, therapeutic, or preventive strategies.

### Cardiac ion channels

To investigate function and regulation of ion channels, a broad range of sophisticated electrophysiological, molecular biological, and cell physiological methods is applied on cultured cells, native tissues, animal models

(e.g. transgenic mouse lines), and human cells. For example, the patch-clamp technique allows for a detailed analysis of membrane potential and ion channel function by electrically controlling individual cardiac myocytes. Ion channels are particularly important in shaping the action potential and in initiating the contraction. It is well established that regional differences in action potential duration (APD) in different areas of the heart are of great importance for a normal course of repolarization. For example, within the left ventricular free wall, APD is much longer in endocardial than in epicardial myocytes with the consequence that endocardial myocytes repolarize last, although they become depolarized first. Hence, the wave of excitation travels from endocardial to epicardial regions, while the wave of repolarization travels in the opposite direction. Under pathological conditions, such as cardiac hypertrophy or failure, this well-organized sequence of events is altered which is thought to contribute to the increased risk of cardiac arrhythmia and sudden cardiac death of patients with cardiac hypertrophy or failure. In order to further understand the underlying mechanisms, our research group investigates the regulation and pharmacology of ion channels (Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>2+</sup> channels) that are responsible for cardiac excitation and repolarization by using animal models as well as tissue or cell culture. At present, the primary focus lies in the identification of signaling cascades that participate in the regulation of those ion channels under pathophysiological conditions. A promising target is the cardiac mineralocorticoid receptor that participates in the regulation of cardiac Ca<sup>2+</sup> and K<sup>+</sup> channels.

It is hoped that a more detailed characterization of cardiac ion channels will lead to a better understanding of the mechanisms underlying cardiac repolarization and will help to develop therapeutic strategies to influence the organization of repolarization and hence prevent the development of malignant arrhythmia.



Isolated human ventricular cardiomyocyte during patch-clamp recording

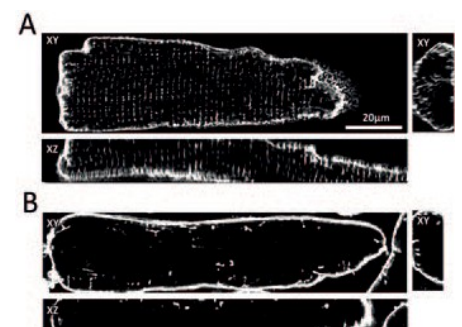
### Electromechanical coupling

Electromechanical coupling is the process that links electrical signals from the cell membrane, i.e. action potentials, to the mechanical action of

the cell, i.e. the contraction. In the heart, a Ca<sup>2+</sup>-influx into the cell via L-type Ca<sup>2+</sup> channels activates ryanodine receptors located intracellularly in the sarcoplasmic reticulum (SR) which in turn release much more Ca<sup>2+</sup> from the SR. This process, called Ca<sup>2+</sup>-induced Ca<sup>2+</sup>-release, activates contraction and controls its magnitude. For example, when not enough Ca<sup>2+</sup> is released from the SR or the release is too slow, the resulting contraction is inefficient and weak. Multiple mechanisms can cause alterations in electromechanical coupling. In heart failure, alterations in the microarchitecture of cardiac myocytes particularly contribute to a decrease in Ca<sup>2+</sup> release from the SR.

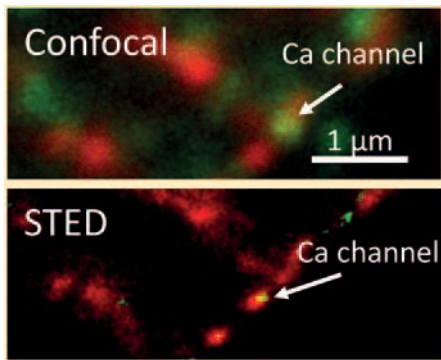
The transverse tubular system (t-system) in ventricular cardiomyocytes consists of many tube-like membrane invaginations that originate from the cell surface and reach deeply into the cell. L-type Ca<sup>2+</sup> channels are primarily localized in the t-tubular membrane in close vicinity to the ryanodine receptors. An important task of t-tubules is therefore to facilitate a close contact of L-type Ca<sup>2+</sup> channels to ryanodine receptors in order to provide the condition for an efficient and quick release of Ca<sup>2+</sup> from the SR. Three dimensional high resolution microscopy (confocal or STED microscopy) reveals that in heart failure, t-system structure and expression of Ca<sup>2+</sup> channels is substantially altered. These alterations lead to delayed, reduced, and disorganized Ca<sup>2+</sup> release from the SR which can also be identified using high resolution microscopy together with Ca<sup>2+</sup> indicators and computer assisted image analysis.

Using cell- and tissue culture models derived from human heart samples, we investigate the cellular and molecular mechanisms underlying t-system alterations with the aim to stop or even reverse these processes. Furthermore, we link structural and functional alterations at the cellular and molecular level to the clinical picture of patients in order to identify prognostic or diagnostic markers or even new therapeutic strategies.



A 3D confocal microscopic image of the t-system in a cardiomyocyte.

B Cardiomyocyte with loss of t-system, e.g. in heart failure



*Immunofluorescence analysis of Ca<sup>2+</sup> channel expression using confocal and STED microscopy in a cardiomyocyte*

Prof. D Alvarez de la Rosa, University of La Laguna, La Laguna: Spain

Dr. R Oakley / Prof. J Cidlowski, National Institute of Health and Environmental Sciences, Research Triangle Park, North Carolina: USA

## Teaching

The Professorship of Cardiovascular Physiology is involved in the curricular teaching (lectures, seminars, and practical classes) for medical and dental students and for students following the degree programs Molecular Medicine (Bachelor and Master).

The Institute provides research opportunities for medical students working towards a doctoral degree and for bachelor, master, and graduate students.

## Selected publications

Launhardt M, Ebel N, Kondruweit M, Weyand M, Volk T, Drummer D. Developing a patient individualized flexible silicone implant using SLS and vacuum die casting. AIP Conference Proceedings 2055. 2019. 140005; <https://doi.org/10.1063/1.5084908>

Seidel T, Fiegle DJ, Baur TJ, Ritzer A, Nay S, Heim C, Weyand M, Milting H, Oakley RH, Cidlowski JA, Volk T. Glucocorticoids Preserve the T-Tubular System in Ventricular Cardiomyocytes by Upregulation of Autophagic Flux. Basic Res Cardiol 2019. 114: 47

Abu-Khousa M, Fiegle DJ, Sommer ST, Minabari G, Milting H, Heim C, Weyand M, Tomasi R, Dendorfer A, Volk T, Seidel T. The Degree of T-System Remodeling Predicts Negative Force-Frequency Relationship and Prolonged Relaxation Time in Failing Human Myocardium. Front Physiol 2020. 11:182

Fiegle DJ, Volk T, Seidel T. Isolation of Human Ventricular Cardiomyocytes from Vibratome-Cut Myocardial Slices. J Vis Exp. 2020. 159: e61167. doi: 10.3791/61167

Wacker C, Dams N, Schauer A, Ritzer A, Volk T, Wagner M. Region-specific mechanisms of corticosteroid-mediated inotropy in rat cardiomyocytes. Sci Rep. 2020. 10:11604. doi: 10.1038/s41598-020-68308-4

Bleisinger N, Dittrich R, Strahl O, Brauweiler R, Hoffmann I, Beckmann WM, Volk T. Me2SO perfusion time for whole-organ cryopreservation can be shortened: results of micro-computed tomography monitoring during Me2SO perfusion of rat hearts. PLOS One. 2020. 15:e0238519. doi: 10.1371/journal.pone.0238519

## International cooperations

Prof. FB Sachse, University of Utah, Salt Lake City, Utah: USA