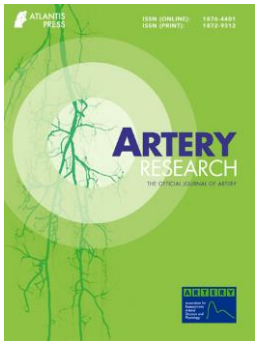

Artery Research

ISSN (Online): 1876-4401 **ISSN (Print): 1872-9312**
Journal Home Page: https://www.atlantis-press.com/journals/artres

9.5: COAGULATION CONTROL BY THE RHOA PATHWAY AND THE EXCHANGE FACTOR ARHGEF1

Camille Rouillon, Amel Mohammadi, Gervaise Loirand, Veronique Regnault, Patrick Lacolley

To cite this article: Camille Rouillon, Amel Mohammadi, Gervaise Loirand, Veronique Regnault, Patrick Lacolley (2016) 9.5: COAGULATION CONTROL BY THE RHOA PATHWAY AND THE EXCHANGE FACTOR ARHGEF1, Artery Research 16:C, 69–69, DOI: https://doi.org/10.1016/j.artres.2016.10.072

To link to this article: https://doi.org/10.1016/j.artres.2016.10.072

Published online: 7 December 2019

high salt diet, with correspondingly greater urine output. Tail-cuff SBP was higher in rats on a high salt diet. There was no left ventricular hypertrophy ($p=0.16$) but greater kidney mass in high salt rats ($p=0.01$). High salt diet resulted in higher aPWV ($p<0.001$ at each 5 mmHg interval) and PPA ($p<0.001$ at each 5 mmHg interval).
Conclusions: High salt diet induced a moderate increase in arterial blood pressure, increased aortic stiffness, and higher PPA, indicating marked changes in transmission characteristics of the aorta including altered stiffness gradient and changed peripheral wave reflection characteristics.

9.4
EVOLUTION OF CARDIAC FUNCTION AND METABOLISM DURING AGING IN A MURINE ANIMAL MODEL OF OBESITY

Delphine Lambert [1], Fatiha Maskali [3], Sylvain Poussier [3], Alexandra Clement [3], Jean-Loup Machu [2], Pierre-Yves Marie [1], Patrick Lacolley [1], Athanase Benetos [1], Laure Joly [1]
[1]*INSERM U1116, Vandoeuvre-les-Nancy, France*
[2]*CIC-P, Vandoeuvre-les-Nancy, France*
[3]*Nancyclotep, Vandoeuvre-les-Nancy, France*

Purpose/Background/Objectives: Obesity is a well-known risk factor of cardiovascular diseases and a potentially modifiable determinant of arterial ageing. The objectives of this experimental study were to assess the effects of a long-term high fat diet (HFD) on metabolism, adipose tissues and phenotypes of cardiovascular aging.
Methods: Murine model chosen was C57BL/6J mice receiving during one year HFD or control diet (CD). Longitudinal follow-up of weight, systolic blood-pressure, heart rate and metabolic parameters was performed. An echocardiographic system was used to study cardiac function. Metabolism at the level of the adipose tissues was studied with FDG positron emission tomography (PET).
Results: After 12 months of diet the whole mice showed a positive correlation between plasma leptin level and left ventricular thickness and mass (both $p<0.05$).
As compared with the CD, the HFD was associated with metabolic disorders: higher body weight, hyperglycemia (both $p<0.01$) and increase in heart rate ($p<0.05$). Despite lack of modification of the systolic blood pressure, the HFD over 12 months increased left ventricular mass ($p<0.01$) and thickness of the inter-ventricular septum ($p<0.05$). Moreover, this parameter was positively correlated to leptin level ($p<0.05$). Finally, we observed in HFD mice a decrease of glucose metabolism in white fat after 6 months and 12 months and in brown fat only after 12 months (both $p<0.01$).
Conclusions: A long term HFD leads to metabolic disorders and to left ventricular morphological changes. The decrease of glucose metabolism observed in brown fat is compatible with an accelerate process of aging by the HFD.

9.5
COAGULATION CONTROL BY THE RHOA PATHWAY AND THE EXCHANGE FACTOR ARHGEF1

Camille Rouillon [1], Amel Mohammadi [1], Gervaise Loirand [2], Veronique Regnault [1], Patrick Lacolley [1]
[1]*UMR S 1116 Defaillance Cardiovasculaire Aigue et Chronique, Nancy, France*
[2]*UMR 1087 Institut du Thorax, Nantes, France*

Platelet activation by thrombin is an auto-amplification loop of thrombin generation, a major factor in the formation of atherosclerotic plaques. The small G protein RhoA, under the direct control of the exchange factor Arhgef1, modulates several cellular functions in inflammation. The objective was to study the RhoA pathway and its control by Arhgef1 in platelet aggregation and thrombin generation due to PAR receptor activation by thrombin.
We used a knockout mouse model for the exchange factor Arhgef1 (Arhgef1 -/-). In response to an agonist (collagen, ADP and thrombin), the expression of surface glycoproteins and the aggregation of washed platelets were not altered in the Arhgef1 -/- mice compared to Argef1 +/+ mice. In contrast, platelet activation studied by the secretion of granules a, exposure to phosphatidylserine and release of microparticles were decreased in the Arhgef1 -/- mice. Thrombin generation in whole platelet-rich blood was also reduced by 25%. These changes result in a lengthening of the time of occurrence of an occlusive thrombus in the carotid induced by $FeCl_3$.
In conclusion, the results confirm the involvement of the RhoA pathway in platelet activation and demonstrate an Arhgef1-dependent mechanism. The results in mice show a new auto-amplification mechanism of thrombin generation by platelets through PAR and membrane phospholipids. Redistribution of phospholipid linked rearrangements of the membrane complex induced by inflammation suggests that the RhoA pathway potentiates the deleterious effects of thrombin in atherothrombosis.
References
1. Ait Aissa, K., Lagrange, J., Mohamadi, A., Louis, H., Houppert, B., Challande, P., Wahl, D., Lacolley, P., And Regnault, V.. Vascular smooth muscle cells are responsible for a prothrombotic phenotype of spontaneously hypertensive rat arteries. Arterioscler. Thromb. Vasc. Biol. 2015, 35: 930—937.
2. Guilluy, C., Brégeon, J., Toumaniantz, G., Rolli-Derkinderen, M., Retailleau, K., Loufrani, L., Henrion, D., Scalbert, E., Bril, A., Torres, R.M., Et Al.. The Rho exchange factor Arhgef1 mediates the effects of angiotensin II on vascular tone and blood pressure. Nat. Med. 2010, 16: 183—190.
3. Jin, J., Mao, Y., Thomas, D., Kim, S., Daniel, J.L., And Kunapuli, S.P. RhoA downstream of G(q) and G(12/13) pathways regulates protease-activated receptor-mediated dense granule release in platelets. Biochem. Pharmacol. 2009, 77: 835—844.
4. Loirand, G., Sauzeau, V., And Pacaud, P. Small G proteins in the cardiovascular system: physiological and pathological aspects. Physiol. Rev. 2013, 93: 1659—1720.
Pleines, I., Hagedorn, I., Gupta, S., May, F., Chakarova, L., Van Hengel, J., Offermanns, S., Krohne, G., Kleinschnitz, C., Brakebusch, C., Et Al. Megakaryocyte-specific RhoA deficiency causes macrothrombocytopenia and defective platelet activation in hemostasis and thrombosis. Blood 2012, 119: 1054—1063.

9.6
VENTRICULAR VOLUME AND ARTERIAL FLOW DURING PRELOAD REDUCTION: AN MRI STUDY

Sandra Neumann [1], Gergely Szantho [3], Emma C. Hart [1], Nathan E. Manghat [2], Mark S. Turner [3], Mark C. K. Hamilton [2]
[1]*University of Bristol, UK*
[2]*Department of Clinical Radiology, Bristol Royal Infirmary, Bristol, UK*
[3]*Department of Cardiology, Bristol Royal Infirmary, Bristol, UK*

Lower body negative pressure (LBNP) has been used to assess the cardiovascular effect of preload reduction. We are the first to use MRI to investigate ventricular volumes and great vessel flow during LBNP.
13 volunteers (23-47years) underwent LBNP at 0, -5 and -20mmHg. We acquired contiguous short axis steady state free precession cine images (8mm slices) of both ventricles during relaxed expiratory breath hold, and flow images with free breathing phase contrast MR angiography of the ascending aorta (Ao) and main pulmonary trunk (MPA).
Analysis was performed using Argus software (Siemens Medical Solutions), statistical assessment by one-way ANOVA and Bonferroni post hoc tests with p-values adjusted for multiple comparisons.
At 5mmHg, no change in Ao flow, velocity or left ventricular (LV) volumes was seen. Diastolic blood pressure (DBP) increased ($p=0.04$). Right ventricular (RV) output ($p=0.01$) and MPA flow ($p=0.03$) was decreased.
At 20mmHg, Ao flow ($p<0.0001$) and velocity ($p=0.0005$) were decreased. Ao retrograde flow increased ($p=0.04$). LV stroke volume (SV, $p=0.0005$), ejection fraction (EF, $p=0.02$) and end diastolic volume (EDV, $p<0.0001$) decreased. DBP increased ($p=0.02$). MPA flow ($p<0.0001$) and velocity ($p<0.0001$) decreased, with no change in retrograde flow. RV EDV ($p<0.0001$) and ESV ($p=0.02$) reduced.
Our data implies (1) that at 5 mmHg LBNP there is an increased left to left shunt likely via the bronchial circulation to explain the different LV/Ao and RV/MPA response (2) different vasoconstrictive response in the systemic vs. pulmonary circulation to explain the differences in retrograde flow.