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# *Impaired coronary flow reserve by hyperviscosity in a mouse model of non-light chain multiple myeloma – a new mechanism of cardiovascular toxicity*

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**Short summary:**

Multiple myeloma (MM) is associated with increased cardiovascular morbidity and mortality, although the exact underlying mechanisms are unknown. Here we tested the hypothesis that MM impairs coronary flow reserve due to increased blood viscosity caused by elevated monoclonal protein concentration. In a mouse Vκ*MYC model of non-light chain MM recapitulating all aspects of human disease we showed that the disease progression was associated with progressive increase of blood and plasma viscosity. Using intravital microscopy imaging of ex vivo stained red blood cells we observed reduction of coronary flow reserve (CFR) in vivo with the CFR limiting site being coronary capillaries. This was further confirmed by similar coronary flow profile in mice with hyperviscosity induced by acute hyperlipidemia and disappearance of this MM-related CFR impairment in

saline perfused ex vivo hearts. Of note, nitric oxide production in vivo was increased in the coronary circulation, especially at the capillary level, but the systemic concentration of nitric oxide metabolites was unchanged, again supporting the hypothesis that increased blood viscosity is the main culprit here. Moreover, MM progression was associated with progressive impairment of left and right ventricular function, but without histological signs of myocardial deterioration, hypertrophy or fibrosis. Our study shows a potentially completely new mechanism of cardiovascular adverse effects caused by MM or more broadly by hyperviscosity syndromes, i.e., CFR impairment at the capillary level. Since capillaries, unlike larger vessels, cannot be recanalized or dilated, completely new preventive approaches are needed, such as agents affecting blood rheology.

## Biosketch:

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Główne zainteresowania naukowe: patofizjologia chorób układu krążenia, szczególnie niewydolności serca, nadciśnienia płucnego, niedokrwienia mięśnia sercowego. Pracuje zarówno na modelach zwierzęcych (zawał mięśnia sercowego, zwężenie tętnicy płucnej u szczura), jak i na materiale ludzkim (ZFK posiada biobank serc ludzkich obejmujących tkanki i komórki izolowane z serc niewydolnych i zdrowych).

## Relevant publications:


1. Oknińska, M, Zajda, K, Zambrowska, Z, Grzanka, M, Paterek, A, Mackiewicz, U, Szczylik, C, Kurzyna, M, Piekiełko-Witkowska, A, Torbicki, A, Kieda, C, Mączewski, M. Role of Oxygen Starvation in Right Ventricular Decompensation and Failure in Pulmonary Arterial Hypertension. JACC: Heart Failure 2024;12:235-247.
2. Załęska-Kocięcka, M, Wojdyńska, Z, Kalisz, M, Litwiniuk, A, Mączewski, M, Leszek, P, Paterek, A. Epicardial fat and ventricular arrhythmias. Heart Rhythm 2024;21:206-212.
3. Oknińska, M, Paterek, A, Grzanka, M, Zajda, K, Surzykiewicz, M, Rolski, F, Zambrowska, Z, Torbicki, A, Kurzyna, M, Kieda, C, Piekiełko-Witkowska, A, Mączewski, M. Myo-inositol trispyrophosphate prevents right ventricular failure and improves survival in monocrotaline-induced pulmonary hypertension in the rat. British Journal of Pharmacology 2024;181:4050-4066.
4. Paterek, A, Załęska-Kocięcka, M, Wojdyńska, Z, Kalisz, M, Litwiniuk, A, Leszek, P, Mączewski, M. Epicardial fat in heart failure - friend, foe or bystander. Obesity Reviews 2024;25:e13820.

5. Paterek, A, Oknińska, M, Pilch, Z, Sosnowska, A, Ramji, K, Mackiewicz, U, Golab, J, Nowis, D, Mączewski, M. Arginase Inhibition Mitigates Bortezomib-Exacerbated Cardiotoxicity in Multiple Myeloma. Cancers 2023;15.

6. Vausort, M, Niedolistek, M, Lumley, AI, Oknińska, M, Paterek, A, Mączewski, M, Dong, X, Jäger, C, Linster, CL, Leszek, P, Devaux, Y. Regulation of N6-Methyladenosine after Myocardial Infarction. Cells 2022;11:2271.

7. Paterek, A, Sochanowicz, B, Oknińska, M, Śmigielski, W, Kruszewski, M, Mackiewicz, U, Mączewski, M, Leszek, P. Ivabradine prevents deleterious effects of dopamine therapy in heart failure: No role for HCN4 overexpression. Biomedicine & Pharmacotherapy 2021;136:111250.