Göteborg, 2019

Cardiac abnormalities in chronic kidney disease

- an investigation of pathophysiological mechanisms

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs universitet kommer att offentligen försvaras i
Hjärtats aula, Vita stråket 12, Sahlgrenska Universitetssjukhuset,
Fredagen den 13 december 2019 kl 09.00

av Pavlos Kashioulis

Fakultetsopponent:

Jonas Spaak, Docent i kardiologi, hjärtkliniken Danderyd sjukhus samt Institutionen för kliniska vetenskaper, Danderyds sjukhus, Karolinska Institutet

Avhandlingen baseras på följande delarbeten

I. Kashioulis P, Hammarsten O, Marcussen N, Shubbar E, Saeed A, Guron G. High-NaCl Diet Aggravates Cardiac Injury in Rats with Adenine-Induced Chronic Renal Failure and Increases Serum Troponin T Levels. *Cardiorenal Med. 2016 Aug;6(4):317-27*

II. Kashioulis P, Lundgren J, Shubbar E, Nguy L, Saeed A, Guron CW, Guron G. Adenine-Induced Chronic Renal Failure in Rats: A Model of Chronic Renocardiac Syndrome with Left Ventricular Diastolic Dysfunction but Preserved Ejection Fraction. *Kidney Blood Press Res. 2018;43(4):1053-1064*

III. Kashioulis P, Guron CW, Svensson M, Hammarsten O, Saeed A, Guron G. Patients with chronic kidney disease stages 3 and 4, without known heart disease, show echocardiographic abnormalities in left ventricular diastolic function and reduced coronary flow velocity reserve. *In manuscript*.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN

GÖTEBORGS UNIVERSITET

Göteborg, 2019

Cardiac abnormalities in chronic kidney disease - an investigation of pathophysiological mechanisms

Pavlos Kashioulis

Department of Molecular and Clinical Medicine, Institute of Medicine Sahlgrenska academy, University of Gothenburg, Sweden, 2019.

Abstract

Chronic kidney disease (CKD) is a global health problem associated with increased risk of mortality and development of end-stage renal disease (ESRD). Cardiovascular diseases are the leading cause of morbidity and mortality even before the development of ESRD. The main purpose of this thesis is to elucidate pathophysiological mechanisms causing cardiac injury in patients with CKD. The specific aims were: 1) To examine the effects of two weeks of high NaCl diet on left ventricular (LV) morphology and serum levels of cardiac troponin-T (cTnT) in rats with adenine-induced chronic renal failure (ACRF). 2) To determine the effects of ACRF on cardiac morphology and function and to examine mechanisms causing cardiac abnormalities. 3) To identify early, sub-clinical, cardiac abnormalities by echocardiography in patients with CKD stages 3 and 4 and to investigate mechanisms that might cause these alterations. *Paper 1*. Rats with ACRF showed statistically significant increases in arterial pressure (AP), LV weight and fibrosis, and serum cTnT levels compared to controls. Two weeks of high-NaCl intake augmented the increases in AP, LV weight, fibrosis, and serum cTnT concentrations only in ACRF rats and produced LV injury with cardiomyocyte necrosis, scarring, and fibrinoid necrosis of small arteries. *Paper 2*. Cardiac function was assessed both by echocardiography and by LV catheterization. ACRF rats developed LV hypertrophy and showed signs of LV diastolic dysfunction but systolic function and cardiac output were preserved. *Paper 3*. In a cohort of patients with CKD stages 3 and 4, and matched controls, we performed comprehensive investigations including echocardiography and assessment of coronary flow velocity reserve (CFVR) in response to adenosine. CKD patients had normal systolic function but showed signs of LV diastolic dysfunction without fulfilling criteria for heart failure with preserved ejection fraction. In addition, CKD patients had significantly reduced CFVR versus controls suggestive of coronary microvascular dysfunction (CMD) In conclusion, ACRF rats developed LV hypertrophy and diastolic dysfunction while systolic performance was preserved. High-NaCl diet in rats with ACRF produced severe LV injury and aggravated increases in serum cTnT levels, presumably by causing hypertension-induced small artery lesions leading to myocardial ischemia. These results support the hypothesis that a high dietary intake of NaCl has deleterious effects on LV integrity in patients with kidney failure. Patients with CKD stages 3 and 4, without a diagnosis of heart disease, showed signs of LV diastolic dysfunction and a relatively large proportion had CMD suggesting that microvascular abnormalities may have a pathogenic role in the development of heart failure in this patient group.

Keywords: cardiovascular, chronic kidney disease, diastolic dysfunction

ISBN: 978-91-7833-656-2 (TRYCK)
ISBN: 978-91-7833-657-9 (PDF)
http://hdl.handle.net/2077/60819