International Journal of Cardiology 184 (2015) 710–716

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Interrelated aldosterone and parathyroid hormone mutually modify cardiovascular mortality risk☆

Andreas Tomaschitz [a,b,c,*], Stefan Pilz [d,e,**], Jutta Rus-Machan [a], Andreas Meinitzer [f], Vincent M. Brandenburg [g], Hubert Scharnagl [f], Martin Kapl [b], Tanja Grammer [h], Eberhard Ritz [i], Jörg H. Horina [j], Marcus E. Kleber [h], Burkert Pieske [b,c], Elisabeth Kraigher-Krainer [b,c], Bríain ó Hartaigh [k,l], Hermann Toplak [m], Adriana J. van Ballegooijen [e], Karin Amrein [d], Astrid Fahrleitner-Pammer [d], Winfried März [f,h,n]

[a] Specialist Clinic for Rehabilitation Bad Aussee, Bad Aussee, Austria
[b] Department of Cardiology, Medical University of Graz, Graz, Austria
[c] Department of Internal Medicine - Cardiology, Charité University Hospital Berlin, Campus Virchow Klinikum, Berlin Germany
[d] Department of Internal Medicine, Division of Endocrinology and Metabolism, Medical University of Graz, Graz, Austria
[e] Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Center, 1081 BT Amsterdam, The Netherlands
[f] Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria
[g] Department of Cardiology, University Hospital of the RWTH, Aachen, Germany
[h] Vth Department of Medicine (Nephrology, Hypertensiology, Endocrinology, Diabetology, Rheumatology), Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany
[i] University Hospital Heidelberg, Department of Medicine, Division of Nephrology, Heidelberg, Germany
[j] Department of Internal Medicine, Division of Nephrology, Medical University of Graz, Graz, Austria
[k] Department of Radiology, Dalio Institute of Cardiovascular Imaging, New York-Presbyterian Hospital and the Weill Cornell Medical College, New York, USA
[l] Department of Internal Medicine, Section of Geriatrics, Yale School of Medicine, Adler Geriatric Center, New Haven, USA
[m] Department of Internal Medicine, Diabetes and Metabolism, Medical University of Graz, Austria
[n] Synlab Academy, Synlab Services LLC, Mannheim, Germany

ARTICLE INFO

*Article history:*
Received 25 November 2014
Received in revised form 19 January 2015
Accepted 3 March 2015
Available online 4 March 2015

*Keywords:*
Aldosterone
Parathyroid hormone
Cardiovascular mortality

ABSTRACT

*Background:* Inappropriate aldosterone and parathyroid hormone (PTH) secretion is associated with increased cardiovascular risk. Accumulating evidence suggests bidirectional interplay between aldosterone and PTH.
*Methods:* We evaluated the cross-sectional relationship between plasma aldosterone concentration (PAC), aldosterone to renin ratio (ARR) and PTH and subsequently tested whether the interaction between PAC and PTH modified the risk of cardiovascular death.
PAC [78.0 (48.0–123.0) pg/mL], ARR [6.4 (2.9–12.9) pg/mL/pg/mL] and PTH concentration [median: 29.0 (22.0–40.0) pg/mL] were measured in 3074 patients (mean age: 62.5 ± 10.6 years; 30.3% women) referred to coronary angiography in a tertiary care center in Southwest Germany.
*Results:* Using multiple linear regression analysis, PAC and ARR emerged as an independent predictor of higher PTH concentrations ($\beta = 0.12$ and 0.21, $P < 0.001$ for both) irrespective of intake of antihypertensive treatment, 25(OH)D, kidney function, serum calcium, phosphate, magnesium, cortisol, NT-pro-BNP, soluble α-klotho and FGF-23 concentration. After a median follow-up of 9.9 years, 512 (16.7%) participants had died due to fatal cardiovascular events. Multivariate Cox proportional hazard analysis revealed that both PAC and PTH were independently associated with cardiovascular mortality, with a potential synergistic interaction ($P = 0.028$). PAC and PTH are exclusively associated with cardiovascular death in subjects with PTH and PAC concentrations above the median, respectively (PAC: HR per log SD: 1.14; 95% CI 1.02–1.29; $P = 0.026$; PTH: HR per log SD: 1.18; 95% CI 1.02–1.37; $P = 0.031$).
*Conclusions:* Higher PAC and ARR were independently associated with PTH. PAC was independently related to incident cardiovascular mortality exclusively in patients with elevated PTH and vice versa.


☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
* Correspondence to: A. Tomaschitz, Department of Cardiology, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria.
** Correspondence to: S. Pilz, Department of Internal Medicine, Division of Endocrinology and Metabolism, Auenbruggerplatz 15, 8036 Graz, Austria.
*E-mail addresses:* andreas.tomaschitz@gmx.at, andreas.tomaschitz@medunigraz.at (A. Tomaschitz), stefan.pilz@chello.at, stefan.pilz@medunigraz.at (S. Pilz).

http://dx.doi.org/10.1016/j.ijcard.2015.03.062
0167-5273/

## 1. Introduction

Dysregulation of aldosterone as well as parathyroid hormone (PTH) has previously been recognized to play a pivotal role in the development and progression of vascular and myocardial diseases [1,2]. Growing evidence points to a clinically relevant reciprocal interaction between these two hormones, which might aggravate cardiovascular (CV) damage [3,4].

PTH increases the secretion of aldosterone from the adrenals directly as well as indirectly by activating the renin–angiotensin system (RAS) [5,6]. In chronic heart failure, secondary hyperaldosteronism causes salt retention and secondary hyperparathyroidism (HPT) due to urinary and fecal losses of calcium and magnesium [7]. In the setting of primary aldosteronism (PA), urinary calcium excretion triggers increased PTH secretion, which in turn, aggravates aldosterone secretion, resulting in vascular damage [8]. This sequence explains why (1) adrenalectomy and blockade of the mineralocorticoid receptor (MR) tend to decrease PTH levels in patients with elevated aldosterone and (2) parathyroidectomy is followed by decreased calcium, renin, and aldosterone levels [8,9].

In view of the reciprocal interaction between aldosterone and PTH and the potentially ensuing CV damage, studies are necessary to evaluate the mechanisms and modulators behind this interplay and its impact on CVD outcomes in humans with proper adjustments for potential confounders. Understanding the impact of the PTH-aldosterone interaction on CV risk may provide additional insight into the complex mechanisms of CVD development and could lead to novel treatment strategies. Thus, using cross-sectional and longitudinal data from the LUdwigshafen RIsk and Cardiovascular Health (LURIC) study, we examined the relationship between plasma aldosterone concentration (PAC), aldosterone to renin ratio (ARR) and PTH concentration and tested the hypothesis that the interplay between both hormones impacts on risk of CV death.

## 2. Materials and methods

### 2.1. Study population

The LURIC study is an ongoing prospective cohort study designed to investigate environmental and genetic risk factors of CVD [10]. A total of 3316 Caucasian patients hospitalized for coronary angiography were enrolled between June 1997 and May 2001.

Recruitment was performed consecutively on regular working days. Inclusion criteria were availability of a coronary angiogram, Caucasians of German ancestry to limit genetic heterogeneity, and clinical stability, with the exception of acute coronary syndromes (ACS). Coronary angiography was performed as part of the clinical routine and indications were mainly chest pain or non-invasive tests consistent with myocardial ischemia. Coronary artery disease (CAD) was defined as the occurrence of 1, 2 and 3 vessel diseases. Participants with a history of malignancy within the past 5 years, or any predominant non-cardiac disease were excluded from the study. The LURIC study was approved by the ethics committee at the "Landesärztekammer-Rheinland-Pfalz" (Mainz, Germany), and written informed consent was obtained from all participants. The LURIC study complies with the Declaration of Helsinki.

### 2.2. Demographic and laboratory measurements

Blood samples were drawn (in the supine position) by venous puncture in the morning before cardiac catheterization, after subjects had fasted. Routine laboratory parameters were immediately measured on a daily basis as reported previously [10].

PAC, ARR and serum PTH were available for 3074 participants. PAC was determined using radioimmunoassay (Active aldosterone; Diagnostic Systems Laboratories, www.beckmancoulter.com). Intra- and inter-assay coefficients of variation were 3.6%–8.3% and 7.3%–10.4%, respectively. The reference interval is stated as 30–160 pg/mL. Intact PTH was determined in serum by ElectroChemiLuminescence Immunoassay (ECLIA) on an Elecsys 2010 (Roche Diagnostics, Mannheim, Germany), with a normal range of 15–65 pg/mL and an inter-assay coefficient of variation of 5.7–6.3%. Plasma renin concentrations (PRC, reference range, 3–28 pg/mL in supine position) were measured using an immunoradiometric assay (Active Renin; Nichols Institute Diagnostics). The ARR was calculated according to Trenkel et al., who proposed a ratio 50 pg/mL/pg/mL as suggestive of PA, with sensitivity and specificity of 89% and 96%, respectively [11]. Serum concentrations of 25-hydroxyvitamin D [25(OH)D] were measured by radioimmunoassay (DiaSorin Antony, France; Stillwater, USA) with intra- and inter-assay coefficients of variation of 8.6 and 9.2%, respectively. N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) was determined by ElectroChemiLuminescence (ECL) on an Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). Fibroblast growth factor 23 (FGF-23, C-term) was measured by enzyme-linked immunosorbent assay (ELISA, Immundiagnostik AG, Bensheim, Germany), intra- and inter-assay coefficients of variation were 2.4 and 3.1%, respectively. Soluble α-klotho was determined by ELISA (Immuno Biological Lab, Fujioka, Japan). High sensitivity C-reactive protein (hsCRP) was measured using immunonephelometry (Dade Behring, Marburg, Germany). The measurement of selected electrolytes in serum (total calcium, magnesium, sodium, phosphate and potassium), free fatty acids, γ-GT, glycated hemoglobin (HbA1c), serum albumin, LDL cholesterol, TSH and serum cortisol concentration has been described previously [10].

Estimated glomerular filtration rate (eGFR) was calculated according to the CKD-EPI study equation. Diabetes mellitus was diagnosed according to the revised recommendations of the American Diabetes Association (ADA). Hypertension was diagnosed (i) if the systolic and/or diastolic BP exceeded 140 and/or 90 mm Hg or (ii) if individuals were on antihypertensive medication: angiotensin-converting enzyme (ACE)-inhibitors, angiotensin-II type-1 (AT1) receptor antagonists, beta-blockers, calcium channel blockers, and/or diuretics. The severity of heart failure was assessed using the NYHA classification. Participants' daily physical activity level was recorded using an 11-point scale and categorized as "below average" (not very active), "average" (usual office work) and "above average" (heavy work or sports).

All patients were on a normal Western diet.

### 2.3. Follow-up

Information on vital status was obtained from local community registries. Death certificates and hospital records were reviewed to classify the deceased into those who died from CV and from non-CV events. Death from CV causes included sudden cardiac death, fatal myocardial infarction, death due to heart failure, death after intervention to treat CAD, stroke and other deaths due to heart disease. The cause of death was unknown for 23 participants. The causes of death were independently classified by two experienced physicians who masked to any of the study data except for information regarding death certificates and hospital records. In case of disagreement concerning classification, it was discussed and the final decision was made by one of the principal investigators of LURIC (W.M.), who was also masked to any data except for the death certificates and hospital records.

### 2.4. Statistical analysis

At baseline, normally distributed continuous variables were reported as means (SD), and variables with non-normal distribution were reported as medians with interquartile ranges. Categorical variables were presented as proportions. For parametric procedures, all non-normally distributed variables were logarithmically (log-10) transformed.

For the overall study sample as well as subgroups according to 25(OH)D status (≥ and <20 μg/L); NT-pBNP (≥ and <median of 282 pg/mL); eGFR (≥ and <60 mL/min per 1.73 $m^2$); diagnosis of CAD; diagnosis of arterial hypertension; antihypertensive treatment; phosphate (≥ and <median of 3.5 mg/dL); and calcium (≥ and <median