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Plasma aldosterone levels are associated with increased cardiovascular mortality: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study

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Aims Evidence has accumulated that elevated aldosterone levels are associated with increased risks of fatal cardiovascular (CV) events. With the present analysis, we aimed at evaluating prospectively whether plasma aldosterone correlates with all-cause and CV disease (CVD) mortality in a large cohort of patients.

Methods and results Median plasma aldosterone concentration (PAC) was 79.0 (48.0–124.0) pg/mL (normal range: 30–160) in 3153 patients [median age: 63.5 (56.3–70.6) years; 30.1% women] who had undergone coronary angiography. After a median follow-up of 7.7 (7.2–8.5) years, a total of 716 participants died [22.7%; 454 (14.4%) due to CV causes and 262 (8.3%) due to non-CV causes]. In multivariable Cox proportional hazard analysis, adjusted for age, gender, antihypertensive treatment, and established CV risk factors, PAC levels stratified in quartiles were significantly associated with all-cause and CVD mortality. Compared with the reference (first) PAC quartile, hazard ratios (confidence interval 95%) for the fourth, third, and second PAC quartiles were 1.30 (1.02–1.65, $P = 0.033$), 1.32 (1.04–1.68, $P = 0.021$), and 1.20 (0.93–1.54, $P = 0.155$) for total mortality and 1.58 (1.15–2.16, $P = 0.004$), 1.39 (1.01–1.90, $P = 0.041$), and 1.63 (1.20–2.20, $P = 0.002$) for CVD mortality, respectively. Analyses for specific causes of CV death revealed strong associations between PAC levels and higher risk for fatal stroke and sudden cardiac death.

Conclusion In a large cohort of patients scheduled for coronary angiography, variation in PAC levels within the normal range is associated with increased all-cause and CVD mortality independent of major established CV risk factors.

Keywords Aldosterone • Cardiovascular mortality

Introduction

Inappropriate activation of the renin–angiotensin–aldosterone system and an inability to lower aldosterone levels in response to the high salt intake in modern societies constitute a maladaptation of this regulatory system. A growing body of evidence suggests that aldosterone contributes to target organ damage beyond its classical role in regulating fluid and electrolyte homeostasis.[1]

Neurohormonal activation in severe heart failure (HF) and in post-myocardial infarction (MI) patients points to a crucial role for aldosterone in the genesis of vascular and myocardial tissue damage.[2,3] Moreover, during the past two decades, substantial evidence has emerged, supporting an independent role of aldosterone in the development of cardiovascular (CV) tissue damage. This includes the evidence from the two landmark studies RALES and EPHESUS, which expanded the indication for

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aldosterone receptor antagonists in chronic HF (CHF).[4–6] These trials documented that mineralocorticoid receptor (MR) blockade in addition to standard care strikingly improves survival of patients with severe symptomatic HF [New York Heart Association (NYHA) III/IV] and systolic left ventricular (LV) dysfunction after acute MI, despite aldosterone levels within the physiological range. Therefore, it has been proposed that the effectiveness of MR blockade in these settings is explained by increased tissue levels of aldosterone, which may be poorly reflected by plasma hormone measurements. Alternatively, it has been suggested that cortisol may activate the MR under circumstances associated with increased oxidative stress.[7–9] Further clinical studies in patients with acute MI and CHF demonstrated that higher concentrations of aldosterone are associated with increased mortality.[7,10–12] Nevertheless, such past studies reporting an association between aldosterone and increased overall CV disease (CVD) mortality were limited by small sample size, short follow-up, and lack of statistically significant relationships between aldosterone and specific causes of CVD mortality. In addition, data concerning the role of aldosterone-mediated CV damage and the effectiveness of MR blockade in patients with mild-to-moderate CHF as well as in those free of acute coronary syndrome (ACS) and LV dysfunction are sparse and derived from small studies and retrospective analyses.[13]

The tantalizing question why MR blockade improves survival in patients despite aldosterone concentrations within the normal range prompted us to prospectively evaluate whether aldosterone levels within the normal range are related to increased CVD mortality. The study included a large cohort of hypertensive and normotensive patients with and without coronary artery disease (CAD), severe HF, and ACS.

Methods

Study design and participants

The Ludwigshafen Risk and Cardiovascular Health (LURIC) study is an ongoing prospective cohort trial designed to investigate the effects of genetic polymorphisms and several biomarkers on the CV system. Study design and baseline examinations have been described previously in detail.[14] In brief, between 1997 and 2000, 3316 Caucasian study participants without major non-CV diseases were referred for coronary angiography to a single tertiary centre and enrolled in the LURIC study. Inclusion criteria were availability of coronary angiogram and stable clinical condition, except for the presence of an ACS. Patients who suffered from any severe non-cardiac disease were excluded. Finally, after exclusion of 29 patients taking an MR blocker, of 18 patients who were lost during follow-up, and of 24 deceased persons for whom we could not obtain the death certificates, 3153 probands in all of whom plasma aldosterone concentration (PAC) had been measured were eligible for analyses.

The LURIC study was approved by the institutional review board at the 'Ärztekammer Rheinland-Pfalz'. Each participant provided written informed consent, and our study complies with the Declaration of Helsinki.

Coronary artery disease was evaluated by coronary angiography based on maximal luminal narrowing of visual stenosis. Adhering to different definitions of CAD, clinically significant CAD was defined as the presence of at least one stenosis $\geq$20% and $\geq$50%, respectively, in at least 1 of 15 coronary segments of the three major coronary arteries. Previous MI was recorded based on a documented history of electrocardiographic ST- and non-ST-elevation and/or elevation of cardiac biomarkers. Acute coronary syndrome was defined as presented in patients within 7 days after the onset of symptoms of unstable angina pectoris, non-ST-elevation MI (troponin T >0.1 μg/L), or ST-elevation MI (troponin T >0.1 μg/L). Systolic and diastolic aortic pressures were measured invasively during coronary angiography. The severity of HF was assessed using the NYHA classification and LV function, which was graded semi-quantitatively by use of contrast ventriculography into 'normal', 'minimally impaired', 'moderately impaired', and 'severely impaired'. Additionally, in 1360 participants, LV ejection fraction (EF), which showed high correlation with semi-quantitative LV function (Spearman's correlation coefficient = −0.834, $P < 0.001$), was calculated from the right anterior oblique view. Dyslipidaemia was defined according to the recommendations of the National Cholesterol Education Program Adult Treatment Panel III as HDL cholesterol <1 mmol/L (40 mg/dL), LDL cholesterol >4.1 mmol/L (160 mg/dL), and/or triglycerides >2.4 mmol/L (200 mg/dL). Glycaemia was assessed by measurement of HbA1c. Type-2 diabetes mellitus was diagnosed if fasting plasma glucose was >1.25 or >2.00 g/L 2 h after an oral glucose load and if the proband was on treatment with oral antidiabetics or insulin. Daily physical activity was assessed by a questionnaire using a scoring system ranging from 1 to 11 [score 1–4: 'below average' (not very active); score 5–7: 'average' (usual office work); and score >7: 'above average' (heavy work or sports)]. Finally, current smoking status and ongoing antihypertensive treatment [angiotensin-converting enzyme (ACE)-inhibitors, angiotensin-II type-1 receptor blockers, beta-blockers, calcium channel blockers, and diuretics] were recorded. All patients were on a normal Western diet.

Laboratory analysis

The standard laboratory methods have been described previously in detail.[14] Plasma aldosterone concentration (pg/mL; conversion to pmol/L: ng/L × 2.78) was measured by radioimmunoassay (RIA) (Active Aldosterone, Diagnostic Systems Laboratories, Sinsheim, Germany). Overall correlation between this RIA and other commercial assays ranges between 0.74 and 0.98.[15] The intra-assay and inter-assay coefficients of variation of this assay were 3.6–8.3 and 7.3–10.4%, respectively. The reference interval is given as 30–160 pg/mL. Plasma renin concentration (PRC) was determined by immunoradiometric assay (Active Renin, Nichols Institute Diagnostics, San Juan, Capistrano, CA, USA). The conversion factor for PRC is based on a publication by Trenkel *et al.*:[16] 1.67 μU/mL (=mU/L) renin equals 1 pg/mL (=ng/L) renin. The normal range is given as 3–28 pg/mL in supine position.

The aldosterone-to-renin ratio (ARR) was calculated as PAC to PRC ratio (pg/mL/pg/mL) according to Trenkel *et al.*[16] An ARR >50 (pg/mL/pg/mL) was suggestive of primary aldosteronism (PA), with a sensitivity and specificity of 89% and 96%, respectively.

The measurement of selected biomarkers, representing key pathways implicated in the pathogenesis of CAD and HF [N-terminal pro-B-type natriuretic peptide-1 (NT-pBNP), plasminogen-activator-inhibitor type-1 (PAI-1), fibrinogen, high sensitivity (hs)-C-reactive protein, creatinine, 1,25-dihydroxyvitamin D (1.25(OH)2D), triglycerides, free fatty acids, asymmetric dimethylarginine (ADMA), and HDL and LDL cholesterol], has been described previously.[14]

Follow-up

About 758 deaths (22.9%) had occurred during a median observation time of 7.7 (7.2–8.5) years. After exclusion of 18 patients who were lost during follow-up and of 24 deceased persons for whom we

could not obtain the death certificates, 716 deceased participants with PAC measurement remained eligible for our analysis. Information on mortality was obtained continuously from local person registries. Classification of death from CVD and non-CVD causes was based on detailed independent exploration of death certificates and medical records by two experienced clinicians who were blinded to the study data except for death certificates. Cardiovascular deaths were further categorized as sudden cardiac death (SCD), fatal MI, death due to congestive HF, death immediately after intervention to treat CAD, fatal stroke, and other causes of deaths due to cardiac disease. Sudden cardiac death was defined as a sudden unexpected death either within 1 h of symptom onset or within 24 h of having been observed alive and symptom-free.[17] Non-CVD death was classified into death from fatal infection, fatal cancer, and other (undefined) causes of death. In the case of disagreement about classification, the final decision was made by one of the principal LURIC investigators after appropriate review of the data.

Statistical analysis

Study participants were divided into quartiles of PACs with concentrations of aldosterone ranging from ≤48, 49 to 78, 79 to 123 and ≥124 pg/mL. Clinical and anthropometric characteristics of the participants were compared across PAC quartiles and presented as percentages for categorical data and as medians with inter-quartile ranges or as means with SD for continuous data. In addition, baseline data were compared between survivors and participants who had died due to CVD. Comparisons between PAC quartile groups were performed using the χ^2 test with *P* by linear-for-linear test for categorical data and by using analysis of variance with *P* for trend for continuous data. Hazard ratios (HRs) and 95% confidence intervals (CI) for all-cause and CVD mortality, the primary outcome, were calculated using Cox proportional hazard analysis with backward procedures, and we presented the results of the final step. Hazard ratios for PAC categories were calculated by comparing the data with those of the lowest PAC (reference) quartile. We adjusted for several possible confounders in the Cox proportional hazard analysis using models that included established clinical and biochemical CV risk factors such as age, gender, body mass index (BMI), dyslipidaemia, fibrinogen, hs-C-reactive protein, HbA1c, PAI-1, NT-pBNP, serum sodium, serum potassium, current smoking, creatinine, physical activity, 1.25(OH)2D, free fatty acids, ADMA, CAD, detailed use of antihypertensive medication, and systolic aortic pressure. Additionally, we tested for colinearity. Finally, product terms were included in the multivariate adjusted Cox proportional hazard models to test for interactions in order to examine whether the nature of the associations between PAC quartiles and CVD mortality differs according to the presence or absence of specific subgroups (i.e. CAD and ACS, etc). A *P*-value less than 0.05 was considered statistically significant. All data were analysed using SPSS 16.0 (SPSS, Inc., Chicago, IL, USA). The authors had full access to the data and take responsibility for the integrity hereof. All authors have read and approved the manuscript as written.

Results

Baseline characteristics

Clinical characteristics according to PAC quartiles of the entire patient cohort are presented in *Table 1*. The median age of the 3153 study participants (30.1% women) was 63.5 (56.3–70.6) years, and the median PAC level was 79.0 (48.0–124.0) pg/mL. About 2427 (77%) and 2105 (66.8%) of the participants revealed significant CAD (presence of 20 and 50% visual stenosis of at least 1 of 15 coronary segments, respectively); 951 (30.2%) patients presented with an ACS. Left ventricular function assessed in 2982 probands by contrast ventriculography revealed normal LV function in 2104 (70.6%) subjects [median LVEF: 71.0 (64.0–77.0)], minimally impaired LV function in 323 (10.8%) subjects [median LVEF: 50.0 (47.0–55.0)], moderately impaired LV function in 362 (12.1%) subjects [median LVEF: 40.0 (37.0–44.0)], and severely impaired LV function in 193 (6.5%) subjects [median LVEF: 28.0 (22.0–33.0)]. Overall, 98 participants (3.1% of the entire cohort) had an ARR ≥50 pg/mL/pg/mL, the threshold value above which PA should be diagnosed according to Trenkel *et al.*[16] who used the same renin assay system as in our study. Baseline characteristics in survivors and individuals who deceased because of fatal CVD events are compared in *Table 2*.

Mortality rates

After a median follow-up of 7.7 (7.2–8.5) years, a total of 716 participants (22.7%) with PAC measurements at baseline had died. Of these, 454 (14.4%) deaths were from CVD [39 (1.24%) fatal stroke, 179 (5.7%) SCD, 86 (2.7%) MI, 109 (3.5%) congestive HF, 23 (0.7%) died after intervention to treat coronary heart disease, and 18 (0.6%) due to other causes of death associated with coronary heart disease] and 262 (8.3%) died due to non-CV causes [54 (1.7%) fatal infection, 92 (2.9%) cancer, and 116 (3.0%) due to other causes], respectively. Only 71 CVD deceased individuals (15.6%) had PAC levels above the upper limit of normal and only 8 (1.8%) participants demonstrated an ARR above 50 pg/mL/pg/mL, a suggested cut-off for PA.

Mortality analyses

Compared with subjects in the lowest (first) quartile of PAC, the multivariate adjusted HRs for death from all causes (adjusted for age, gender, antihypertensive treatment, and selected biomarkers of CVD) were 1.30 (1.02–1.65, $P = 0.033$), 1.32 (1.04–1.68, $P = 0.021$), and 1.20 (0.93–1.54, $P = 0.155$) in the second, third, and fourth PAC quartiles, respectively. Further analyses for specific non-CVD causes of death (fatal infection and fatal cancer) revealed no statistically significant associations with aldosterone.

Table 3 summarizes the findings of the unadjusted and multivariable Cox proportional HR analyses assessing the risk of CVD mortality according to quartiles of PAC (first PAC quartile as reference) including established CVD risk factors in four statistical models. In the multivariate adjusted model, PAC levels within the second, third, and fourth quartiles showed strong associations with a higher risk for fatal CVD events compared with the first (reference) quartile. Accordingly, aldosterone as a continuous variable was positively associated with the incidence rate of fatal CVD events. Detailed adjustment for the use of ACE-inhibitors, angiotensin-II type-1 receptor blockers, beta-blockers, calcium channel blockers, and diuretics did not materially change our results.

Further significant and independent associations with CVD mortality were revealed for age, fibrinogen, HbA1c, CAD, ADMA, free fatty acids, and NT-pro-BNP levels. These parameters were positively and creatinine as well as 1.25(OH)2D were inversely associated with CVD mortality, respectively. Body mass index, dyslipidaemia, current smoking, serum sodium/potassium, PAI-1,

Table 1 Baseline characteristics according to plasma aldosterone concentration quartiles

Variable	Quartile 1 (≤48 pg/mL), *n* = 798	Quartile 2 (49–78 pg/mL), *n* = 774	Quartile 3 (79–123 pg/mL), *n* = 792	Quartile 4 (≥124 pg/mL), *n* = 789	*P* trend
PAC (pg/mL)	34.0 (26.0–42.0)	62.0 (55.0–92.0)	98.0 (87.0–110.0)	169.0 (141.0–221.0)	<0.001
PRC (pg/mL)	8.4 (4.8–18.6)	10.2 (6.0–21.0)	12.0 (6.0–23.4)	19.2 (8.4–22.6)	<0.001
ARR (pg/mL/pg/mL)	3.8 (1.7–7.1)	5.8 (2.9–10.8)	8.3 (4.2–15.9)	10.3 (4.3–21.2)	<0.001
Age (years)	64.1 (57.3–71.7)	63.4 (56.5–70.3)	63.2 (55.7–69.8)	62.3 (54.0–69.7)	<0.001
Female sex (%)	29.8	29.1	28.3	33.2	0.202
Body mass index (kg/m^2)	27.2 ± 4.0	27.6 ± 4.1	27.4 ± 4.0	27.8 ± 4.3	0.040
Triglycerides (mg/dL)	135.5 (103.0–186.2)	139.0 (102.0–194.5)	146.5 (111.2–194.0)	156.0 (113.0–223.0)	<0.001
LDL cholesterol (mg/dL)	112.3 ± 33.2	117.3 ± 33.9	119.4 ± 34.2	119.5 ± 35.6	<0.001
HDL cholesterol (mg/dL)	37.4 ± 10.6	38.6 ± 10.6	39.8 ± 10.7	39.5 ± 11.1	<0.001
Free fatty acids (mmol/L)	0.65 (0.45–0.91)	0.59 (0.41–0.86)	0.59 (0.41–0.85)	0.65 (0.46–0.91)	<0.001
Dyslipidaemia (%)	68.5	66.5	67.7	71.7	0.150
Daily physical activity (%)					
Below average	27.3	23.4	25.1	26.7	0.393
Average	52.7	53.8	53.1	57.1	0.058
Above average	20.0	22.8	21.8	16.2	0.568
ADMA (μmol/L)	0.82 (0.74–0.92)	0.79 (0.72–0.88)	0.80 (0.72–0.90)	0.82 (0.73–0.92)	0.002
PAI-1 (U/mL)	16.0 (9.0–29.0)	16.0 (9.0–32.0)	19.0 (10.0–35.0)	24.0 (13.0–41.7)	<0.001
Fibrinogen (mg/dL)	395.0 (330.0–476.5)	380.0 (320.0–454.0)	365.0 (312.0–432.0)	370.0 (316.0–436.0)	<0.001
Current smokers (%)	21.4	19.3	18.8	19.4	0.297
Type 2 diabetes mellitus (%)	31.7	30.9	32.7	32.6	0.553
HbA1c (%)	6.0 (5.6–6.6)	6.0 (5.6–6.6)	6.0 (5.6–6.6)	6.0 (5.6–6.6)	0.970
Arterial hypertension (%)	56.1	54.7	58.7	64.0	<0.001
Systolic aortic pressure (mmHg)	140.0 (120.0–160.0)	140.0 (125.0–160.0)	140.0 (125.0–160.0)	140.0 (125.0–160.0)	0.421
Diastolic aortic pressure (mmHg)	70.0 (60.0–80.0)	70.0 (65.0–80.0)	75.0 (65.0–80.0)	75.0 (65.0–80.0)	<0.004
History of myocardial infarction (%)	45.9	42.5	37.1	37.5	<0.001
ACS (%)	44.4	31.4	24.1	20.7	<0.001
Coronary artery disease (%)					
20% visual stenosis	81.8	78.7	74.1	74.7	<0.001
50% visual stenosis	72.1	69.2	64.2	65.5	0.001
Antihypertensive treatment (%)	89.5	86.8	83.5	86.2	0.014
ACE inhibitors (%)	59.1	53.0	49.1	49.2	<0.001
ARB (%)	3.9	4.5	4.0	5.7	0.133
Beta-blockers (%)	69.5	63.3	59.3	59.1	<0.001
Calcium channel blockers (%)	11.3	16.5	19.4	16.1	0.003
Diuretics (%)	24.1	24.7	26.6	39.5	<0.001
Creatinine (mg/dL)	0.90 (0.80–1.00)	0.90 (0.80–1.00)	0.90 (0.80–1.10)	0.90 (0.80–1.10)	<0.001
NYHA classification (%)					
1	56.3	53.0	53.7	46.1	<0.001
2	25.1	29.2	30.4	32.8	0.007
3	15.0	14.6	14.3	18.1	0.630
4	3.6	3.2	1.6	2.9	0.712
NT-pBNP (ng/mL)	611.0 (361.0–1327.0)	385.5 (136.2–1048.0)	266.0 (107.7–730.5)	239.0 (87.0–730.0)	0.636
LVEF	60.0 (44.0–71.0)	66.0 (51.2–74.0)	66.5 (58.0–74.7)	64.0 (45.0–75.0)	0.140
1,25–dihydroxyvitamin D (ng/mL)	34.4 ± 13.5	34.7 ± 13.5	36.3 ± 14.0	35.3 ± 15.0	0.053
High-sensitivity C-reactive protein (mg/L)	4.31 (1.54–10.92)	3.29 (1.26–8.43)	2.68 (1.14–6.86)	3.30 (1.32–7.56)	<0.001

Continued

Table 1 *Continued*

Variable	Quartile 1 (≤48 pg/mL), *n* = 798	Quartile 2 (49–78 pg/mL), *n* = 774	Quartile 3 (79–123 pg/mL), *n* = 792	Quartile 4 (≥124 pg/mL), *n* = 789	*P* trend
Plasma cortisol (mg/L)	20.2 (15.7–24.4)	21.0 (17.0–25.6)	22.5 (18.3–26.9)	25.0 (20.0–29.5)	<0.001
Serum sodium level (mmol/L)	141.4 ± 2.7	141.5 ± 2.7	141.2 ± 2.7	140.6 ± 3.2	<0.001
Serum potassium level (mmol/L)	4.2 ± 0.3	4.2 ± 0.3	4.2 ± 0.3	4.2 ± 0.4	0.172

Continuous data are given either as median (25th and 75th percentile) or mean with SD and categorical data as percentages.
Group differences (*P* for trend) were calculated by ANOVA for continuous and χ^2 test for categorical variables.
Quartiles are from baseline plasma aldosterone concentration.
PAC, plasma aldosterone concentration; PRC, plasma renin concentration; ARR, aldosterone-to-renin ratio; ADMA, asymmetric dimethylarginine; PAI-1, plasminogen-activator-inhibitor type-1; ACE, angiotensin-converting enzyme; ARB, angiotensin-II type-1 receptor blockers.

daily physical activity, antihypertensive medication except for beta-blockers, hs-C-reactive protein, and systolic aortic pressure did not reach statistical significance in the Cox proportional hazard analysis.

In fully adjusted analyses for specific causes of CVD death, patients within the fourth PAC quartile were at increased risks for fatal stroke [HR: 7.02 (1.79–27.46, $P = 0.005$)]. Multivariate analyses for SCD showed significant associations for the second and fourth PAC quartiles compared with the reference quartile 1 [HR fourth quartile: 1.73 (1.02–2.92, $P = 0.041$); HR third quartile: 1.28 (0.74–2.22, $P = 0.377$); and HR second quartile: 1.84 (1.10–3.08, $P = 0.019$)]. Cox proportional hazard analysis for fatal MI, congestive HF, and death after intervention to treat CAD showed no statistically significant relationships to PAC.

In order to examine the putative role of glucocorticoids in CV pathology, we performed the same mortality analysis using plasma cortisol as continuous variable, but overall we could not find significant associations between cortisol levels and mortality from CV [fully adjusted HR 0.99 (0.98–1.01, $P = 0.370$)] or from all causes [fully adjusted HR 0.99 (0.98–1.00, $P = 0.111$)] after adjustment of Cox analyses according to model 4 of *Table 3*.

Subgroup analyses

We performed an analysis of patients with verified CAD, with ACS as well as in probands with moderately and severely impaired LV function (*Table 4*). We noted that PAC remained significantly associated with CVD mortality within these subgroups. Of note, although PAC levels in patients with verified CAD ($n = 2427$) were lower than those in individuals without CAD ($n = 726$) [median PAC: 76.0 (47.0–122.0) vs. 86.0 (53.0–130.0) pg/mL; $P < 0.001$], significant associations between aldosterone and CVD mortality were exclusively found in patients with verified CAD (*Table 4*). The relatively low number of fatal CVD events in patients without verified CAD, however, may have limited our ability to detect statistically significant results within this subgroup.

In patients suffering from ACS [median LVEF: 62.0 (45.0–71.2)], PAC levels were significantly associated with SCD. Within this subgroup (ACS), PAC remained significantly associated with CVD death even after exclusion of patients with moderately or severely impaired LV function [$n = 658$; median LVEF: 67.0 (59.0–74.0); *P* for interaction 0.005]. After exclusion of subjects with ACS, we found that in patients with severe HF [$n = 398$; NYHA III/IV; median LVEF: 52.5 (35.0–71.0); *P* for interaction 0.002], PAC values within the second, third, and fourth quartiles were predictive of CVD death [HR fourth quartile: 3.67 (1.53–8.83, $P = 0.004$); HR third quartile: 2.67 (1.06–6.74, $P = 0.037$); and HR second quartile: 3.21 (1.35–7.61, $P = 0.008$)]. In patients with severe HF (NYHA III/IV) but preserved LV function [$n = 371$; median LVEF: 67.0 (56.0–75.0); *P* for interaction 0.673], PAC within the fourth quartile showed a strong association with CVD mortality [HR 2.85 (1.13–7.19, $P = 0.027$)]. It should however be noted that the interaction was not significant and therefore the relative effect is similar in the subgroups with and without severe HF (NYHA III/IV) with preserved LV function. Consistent associations between PAC and CVD mortality were found even in patients with mild symptomatic HF [NYHA I/II; $n = 2574$; median LVEF: 65.0 (50.0–74.0); *P* for interaction <0.001]: HR fourth quartile: 1.55 (1.04–2.33, $P = 0.032$), HR third quartile: 1.53 (1.04–2.26, $P = 0.031$), and HR second quartile: 1.68 (1.14–2.47, $P = 0.008$). In contrast to non-hypertensives ($n = 1312$), PAC levels significantly correlated with CVD mortality in hypertensive patients ($n = 1841$): HR fourth quartile: 1.64 (1.10–2.44, $P = 0.015$), HR third quartile: 1.39 (0.92–2.08, $P = 0.016$), and HR second quartile: 1.65 (1.12–2.44, $P = 0.012$). However, we found no significant interactions ($P = 0.535$) in fully adjusted analysis, indicating that the association of aldosterone with CVD mortality does not differ significantly according to blood pressure (BP) status.

Comparing patients according to serum sodium levels [median serum sodium: 141.2 (139.0–143.0) mmol/L], we noted that in those with serum sodium levels below the median [$n = 1718$; median PAC: 84.0 (50.0–130.0)], no associations between CVD mortality and PAC were found, whereas in subjects with serum sodium levels above 141.2 mmol/L [$n = 1435$; median PAC: 73.0 (47.0–114.0); $P < 0.001$ compared with PAC below the median], PAC values within both the second and fourth quartiles (*P* for interaction 0.029) were independently related to CVD mortality (*Figure 1*). Sodium levels did not differ significantly between patients with and without CAD ($P = 0.276$) and with and without ACS ($P = 0.221$), respectively.

Discussion

The major result of the present investigation is the finding that PAC is independently associated with CVD and all-cause mortality

Table 2 Baseline characteristics for survivors and patients who died due to cardiovascular disease

Characteristics	Survivors (n = 2437)	CVD deceased (n = 454)	P-value
PAC (pg/mL)	78.0 (48.0–124.0)	80.0 (48.2–123.7)	0.006
PRC (pg/mL)	10.8 (5.4–21.6)	16.8 (7.8–41.4)	<0.001
ARR (pg/mL/pg/mL)	7.9 (3.4–13.7)	4.4 (1.6–9–6)	<0.001
Age, mean (years)	61.7 (54.8–68.8)	69.6 (62.8–74.8)	<0.001
Female sex (%)	31.6	25.8	0.012
Body mass index (kg/m^2)	27.6 ± 4.0	27.4 ± 4.4	0.173
Dyslipidaemia (%)	68.6	70.2	0.481
Free fatty acids (mmol/L)	0.59 (0.42–0.84)	0.74 (0.51–1.06)	<0.001
ADMA (μmol/L)	0.80 (0.72–0.89)	0.85 (0.76–0–0.97)	<0.001
PAI-1 (U/mL)	19.0 (10.0–35.0)	17.0 (9.0–34.0)	0.165
Fibrinogen (mg/dL)	365.0 (313.0–436.0)	413.5 (348.2–491.5)	<0.001
Current smokers (%)	21.4	19.3	0.013
Type-2 diabetes mellitus (%)	27.3	52.1	<0.001
HbA1c (%)	6.0 (5.5–6.4)	6.3 (5.8–7.4)	<0.001
Arterial hypertension (%)	57.0	63.2	0.012
Systolic aortic pressure (mmHg)	140.0 (121.0–160.0)	145.0 (125.0–165.0)	0.329
Diastolic aortic pressure (mmHg)	70.0 (65.0–80.0)	70.0 (60.0–80.0)	0.004
History of myocardial infarction (%)	37.9	55.8	<0.001
ACS (%)	31.2	31.0	0.672
Coronary artery disease (%)			
20% visual stenosis	75.6	90.1	<0.001
50% visual stenosis	64.9	83.6	<0.001
Creatinine (mg/dL)	0.9 (0.8–1.0)	1.0 (0.8–1.1)	<0.001
NYHA classification			
1	56.3	37.0	<0.001
2	29.0	29.5	<0.001
3	12.7	27.1	<0.001
4	2.0	6.4	0.023
LVEF (%)	67.0 (52.5–75.0)	44.0 (32.0–64.2)	<0.001
NT-pBNP	225.0 (89.0–580.0)	919.5 (299.7–2379.7)	<0.001
1,25-dihydroxyvitamin D (ng/mL)	36.1 ± 13.9	30.4 ± 13.7	<0.001
High-sensitivity-C-reactive protein (mg/L)	2.9 (1.2–7.5)	5.3 (2.0–11.4)	<0.001
Serum sodium (mmol/L)	141.3 ± 2.7	140.9 ± 3.2	0.004
Serum potassium (mmol/L)	4.2 ± 0.3	4.2 ± 0.4	0.777

Continuous data are given either as median (25th and 75th percentile) or means with SD and categorical data as percentages.
Group differences were calculated by ANOVA for continuous and χ^2 test for categorical variables.
PAC, plasma aldosterone concentration; PRC, plasma renin concentration; ARR, aldosterone-to-renin ratio; ADMA, asymmetric dimethylarginine; PAI-1, plasminogen-activator-inhibitor type-1; CVD, cardiovascular disease.

in individuals undergoing coronary angiography, even at levels below the threshold suggestive of hyperaldosteronism. Analyses of specific causes of CVD death showed that aldosterone is related to a higher risk of SCD and fatal stroke. Furthermore, when analysing different subgroups, we observed that PAC levels correlated with CVD mortality both in patients with verified CAD and in those suffering from ACS. Associations between PAC and CVD mortality in the setting of ACS remained robust even in patients with normal or minimally impaired LV function and are in agreement with previous observations of a beneficial effect of MR blockade post-MI, irrespective of concurrent systolic HF.[18] We also confirmed previous reports that subjects with impaired LV function are at higher risks for CVD death compared to with those with normal LV function. Finally, PAC was related to CVD mortality even in patients with mild symptomatic HF. The analysis of the relationship between PAC and CVD risk suggests that aldosterone concentrations above 48 pg/mL, the lower limit of normal, may be involved in the genesis of target organ damage.

Previous reports indicated that PA is linked to an increased risk for the development and progression of CVD independent of arterial BP.[19–21] In patients with congestive HF and acute MI, secondary hyperaldosteronism driven by increased renin–angiotensin

Table 3 Hazard ratios for cardiovascular mortality according to plasma aldosterone concentration quartiles

	PAC	Q1	Q2	Q3	Q4
Death due to CVD events, no. (% of the whole sample)	454 (14.4%)	104 (3.3%)	119 (3.8%)	107 (3.4%)	124 (3.9%)
PAC in survivors (pg/mL)[a]	78.0 (48.0–124.0)	35.0 (26.0–42.0)	62.0 (55.0–70.0)	98.0 (87.0–110.0)	169.0 (141.7–221.2)
PAC in deceased (pg/mL)[b]	80.0 (51.0–127.0)	35.0 (26.2–42.0)	61.0 (56.0–68.0)	96.0 (86.0–104.0)	167.5 (141.0–227.7)
	HRs per 10 pg/mL PAC increment		**Statistical model, HRs (95% CI) according to PAC Q1 (reference)**		
Model 1	1.01 (1.01–1.02) $P = 0.001$*	1 (reference)	1.16 (0.89–1.51) $P = 0.263$	1.03 (0.79–1.35) $P = 0.835$	1.20 (0.92–1.56) $P = 0.169$
Model 2	1.02 (1.01–1.02) $P < 0.001$*	1 (reference)	1.25 (0.96–1.62) $P = 0.099$	1.14 (0.87–1.49) $P = 0.355$	1.41 (1.09–1.84) $P = 0.009$*
Model 3	1.01 (1.00–1.02) $P = 0.017$*	1 (reference)	1.59 (1.18–2.13) $P = 0.002$*	1.42 (1.05–1.92) $P = 0.022$*	1.53 (1.13–2.08) $P = 0.006$*
Model 4	1.01 (1.00–1.02) $P = 0.013$*	1 (reference)	1.63 (1.20–2.20) $P = 0.002$*	1.39 (1.01–1.90) $P = 0.041$*	1.58 (1.15–2.16) $P = 0.004$*

Model 1, crude; Model 2, adjusted for age and sex; Model 3, additionally adjusted for BMI, fibrinogen, high-sensitivity C-reactive protein, hbA1c, plasminogen-activator-inhibitor type-1, current smoking, creatinine, daily physical activity, NT-pBNP, dyslipidaemia, 1,25-dihydroxyvitamin D, free fatty acids, asymmetric dimethylarginine, use of ACE-inhibitors, angiotensin-II type-1 receptor blockers, beta-blockers, calcium channel blockers, diuretics, serum sodium, serum potassium, and coronary artery disease; Model 4, additionally adjusted for systolic aortic pressure.
CI, confidence interval; HR, hazard ratio. Q indicates quartiles of baseline plasma aldosterone concentration; CVD, cardiovascular disease.
PAC ([a]in survivors and [b]within CVD deceased patients) values are given as median with inter-quartile range.
*$P < 0.05$; $n = 3153$.

system (RAS) activity is associated with higher mortality.[2,3,7,10–12] In good agreement with such past findings, our data indicate that even a PAC within the putative physiological range may cause severe CV damage. In line with this hypothesis is the finding of Pitt *et al.*,[22] who showed that MR blockade reduces LV hypertrophy in hypertensive patients even at low aldosterone concentrations. In addition to the endocrine action of aldosterone in the circulation, the efficacy of MR blockade may in part also be explained by inhibiting paracrine mineralocorticoid effects. In this context, an activated local production of aldosterone was observed in isolated perfused rat hearts after MI and in human failing ventricles.[23,24] Such paracrine action may not accurately be reflected by plasma aldosterone. Funder and Mihailidou[8] proposed that circulating glucocorticoids levels might activate the MR as a result of increased generation of reactive oxygen species (ROS) under metabolic stress and suggested that beneficial effects of MR blockade may be explained by blocking signalling via activated glucocorticoid–MR complexes rather than by blocking aldosterone-mediated MR activation. In this context, we observed a graded increase in plasma cortisol in parallel to rising PAC, but overall we found no significant impact of plasma cortisol on CVD mortality in contrast to a previous analysis in CHF patients.[7] The association between PAC levels within the normal range and increased CVD mortality is consistent with earlier observations of the effective prevention of coronary pathology by MR blockade, indicating that aldosterone contributes to the genesis of vascular lesions via MR activation.[25] Mineralocorticoid receptor activation has pro-inflammatory, pro-thrombotic, and pro-fibrotic effects, which contribute to the development and progression of endothelial dysfunction, decreased nitric oxide bioavailability, myocardial fibrosis and LV hypertrophy, impaired coronary flow, remodelling of resistance arteries, increased ROS generation, and thrombogenesis.[26] Along this line, beneficial effects of aldosterone blockade on CV pathophysiology have been detected in experimental models and clinical trials.[9,25] The evidence for adverse CV effects of aldosterone has been strengthened by a recently published meta-analysis of clinical trials comprising 10 807 patients in 19 randomized controlled trials, which reported an impressive 20% reduction in all-cause mortality following MR blockade in clinical trials with participants suffering from HF and MI.[27] Classical antihypertensive medication, e.g. ACE-inhibitors or beta-blockers, affects circulating aldosterone levels, but, as our findings indicate, may not significantly interfere with and prevent detrimental aldosterone-mediated effects.

Much of the benefit of MR blockade has been attributed to the reduction of SCD, suggesting that aldosterone increases the sensitivity of cardiac tissue to arrhythmias. This is in line with our findings, which link PAC levels over a broad range to an increased risk for SCD in patients who resemble participants of RALES and EPHESUS in regard of age and gender distribution. Compared with the RALES and EPHESUS studies, on average, the participants in the LURIC had less severe systolic LV dysfunction, suggesting less neurohormonal activation. Pro-arrhythmic properties of aldosterone may be mediated by increased sympathetic drive, decreased heart rate variability, disturbed baroreceptor function, blunted myocardial norepinephrine uptake, and alterations in electrolyte homeostasis.[28] In addition, LV hypertrophy due to pro-fibrotic

Table 4 Hazard ratios for deaths from cardiovascular causes according to plasma aldosterone concentration in patients with verified coronary artery disease, acute coronary syndrome, and moderately or severely impaired left ventricular function, respectively

	Deaths, *n* (%)	Model 1 HR (95% CI)	*P*-value	Model 2 HR (95% CI)	*P*-value	Model 3 HR (95% CI)	*P*-value	Model 4 HR (95% CI)	*P*-value
Verified CAD ($n = 2427$); P for interaction = 0.001									
First quartile	84 (2.7%)	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Second quartile	95 (3.0%)	1.31 (0.99–1.74)	$P = 0.060$	1.35 (1.02–1.79)	$P = 0.038$*	1.48 (1.10–1.99)	$P = 0.009$*	1.51 (1.12–2.04)	$P = 0.007$*
Third quartile	91 (2.9%)	1.25 (0.93–1.67)	$P = 0.132$	1.30 (0.97–1.73)	$P = 0.080$	1.37 (1.02–1.86)	$P = 0.038$*	1.31 (0.96–1.78)	$P = 0.092$
Fourth quartile	99 (3.1%)	1.37 (1.04–1.82)	$P = 0.028$*	1.54 (1.16–2.04)	$P = 0.003$*	1.33 (0.98–1.81)	$P = 0.070$	1.37 (1.00–1.88)	$P = 0.047$*
Per 10 pg/mL PAC		1.01 (1.00–1.02)	$P < 0.001$*	1.01 (1.00–1.02)	$P < 0.001$*	1.01 (1.00–1.02)	$P = 0.075$	1.01 (1.00–1.02)	$P = 0.039$*
ACS ($n = 951$); P for interaction = 0.026									
First quartile	39 (1.2%)	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Second quartile	33 (1.0%)	1.24 (0.78–1.96)	$P = 0.373$	1.26 (0.79–2.00)	$P = 0.329$	1.37 (0.83–2.26)	$P = 0.222$	1.41 (0.85–2.34)	$P = 0.180$
Third quartile	31 (1.0%)	1.52 (0.95–2.44)	$P = 0.080$	1.59 (0.99–2.55)	$P = 0.054$	1.54 (0.93–2.58)	$P = 0.097$	1.48 (0.89–2.47)	$P = 0.132$
Fourth quartile	31 (1.0%)	1.73 (1.08–2.77)	$P = 0.023$*	1.97 (1.23–3.16)	$P = 0.005$*	1.77 (1.05–2.98)	$P = 0.031$*	1.75 (1.04–2.96)	$P = 0.035$*
Per 10 pg/mL PAC		1.01 (1.00–1.02)	$P < 0.001$*	1.01 (1.00–1.02)	$P < 0.001$*	1.02 (1.01–1.03)	$P < 0.001$*	1.02 (1.01–1.03)	$P < 0.001$*
Moderately or severely impaired LV function ($n = 523$); P for interaction < 0.001									
First quartile	35 (1.2%)	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Second quartile	41 (1.0%)	1.61 (1.02–2.52)	$P = 0.040$*	1.68 (1.07–2.63)	$P = 0.025$*	2.24 (1.33–3.77)	$P = 0.003$*	2.27 (1.33–3.88)	$P = 0.003$*
Third quartile	31 (1.0%)	1.14 (0.70–1.84)	$P = 0.607$	1.15 (0.71–1.87)	$P = 0.565$	1.24 (0.70–2.20)	$P = 0.461$	1.27 (0.70–2.29)	$P = 0.428$
Fourth quartile	55 (1.0%)	1.70 (1.23–2.52)	$P = 0.014$*	1.85 (1.21–2.83)	$P = 0.004$*	2.03 (1.18–3.48)	$P = 0.011$*	2.07 (1.18–3.63)	$P = 0.011$*
Per 10 pg/mL PAC		1.02 (1.01–1.03)	$P = 0.006$*	1.02 (1.01–1.03)	$P < 0.001$*	1.01 (1.00–1.03)	$P = 0.111$	1.01 (1.00–1.03)	$P = 0.101$

Adjustments for presented Cox proportional hazard analysis are according to model 4 of *Table 3*.
HR, hazard ratios (95% CI); PAC, plasma aldosterone concentration; CAD, coronary artery disease according to 20% visual stenosis in at least 1 of 15 coronary segments; ACS, acute coronary syndrome; LV, left ventricle.

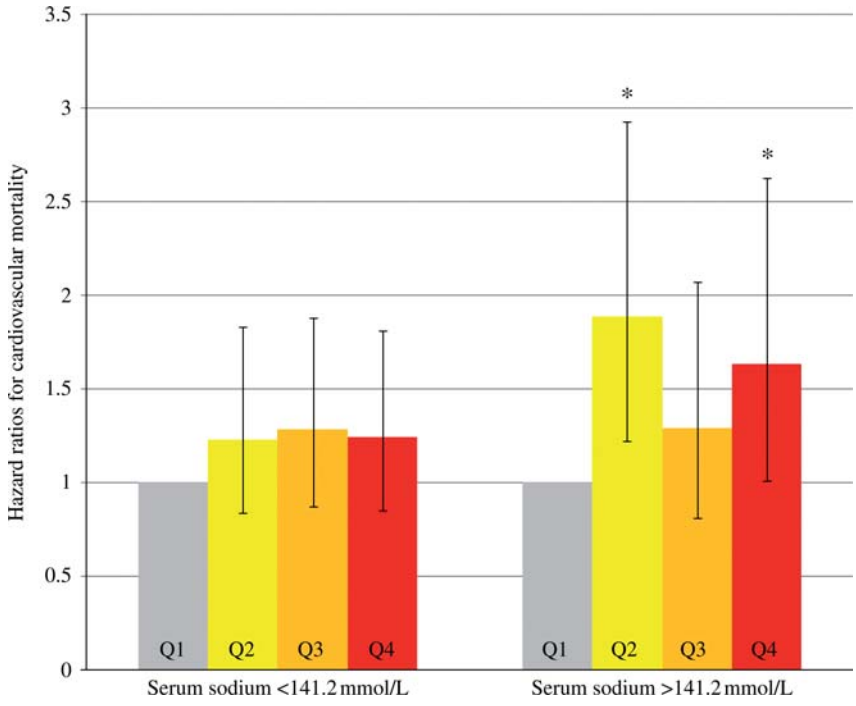

Figure 1 Hazard ratios with 95% confidence intervals for deaths from cardiovascular causes according to plasma aldosterone concentration quartiles (Q) in patients with serum sodium levels below and above the median of 141.2 mmol/L, respectively. Fully adjusted Cox proportional hazard analysis according to model 4 of *Table 3* is illustrated. Asterisk indicates $P < 0.05$

effects of aldosterone is characterized by a diffuse accumulation of connective tissue predisposing the development of profound ventricular arrhythmia via increased electric inhomogeneity of conduction and impaired gap junction function. Finally, aldosterone-mediated MR activation may alter the expression of various ion channels, leading to dysregulations of the cardiac action potential.[29,30] These arguments have been strengthened by the observation of impressive reduction of ventricular extrasystoles and QT intervals after MR blockade.[31]

A variety of experimental studies in rats demonstrated that salt loading is a prerequisite of the adverse coronary and cardiac effects of aldosterone.[32] During evolution, the human species had evolved with, and adapted to, ingestion and excretion of <1 g salt/day, i.e. at least 10 times less than the average amount currently consumed in industrialized areas.[33] Oberleithner *et al.*[34] reported that in human endothelial cell cultures, even small changes in the (physiological) plasma sodium concentration within the range of Western populations on high salt diet (plasma sodium above 135 mmol/L) adversely affected NO production and the mechanical properties of vascular endothelium if high–normal aldosterone concentrations were present. In our cohort, patients with sodium levels above the median of 141.2 mmol/L showed that PAC levels were predictive of CVD mortality, in contrast to patients with sodium levels below 141.2 mmol/L, although it was demonstrated that aldosterone may induce cardiac hypertrophy and severe inflammation even in the absence of salt loading.[35] Absolute PAC levels, however, should be interpreted in relation to concurrent salt status because the two players, i.e. inappropriately high aldosterone concentrations and positive salt balance, apparently underlie the development of endothelial dysfunction and CVD. Apart from the salt status, various factors affect adrenal aldosterone production and responsiveness to aldosterone: posture, age, concomitant medication, genetic variations, and so on. Finally, we also wish to point out that differences between the methods for the determination of plasma aldosterone must be taken into account when using aldosterone as a predictor of CVD events.

Our finding that PAC is exclusively associated in patients with verified CAD is in line with the notion that aldosterone-mediated detrimental effect on the vascular tissue may be in particular pronounced in the setting of pre-existing vascular damage and endothelial dysfunction.[36] In this context, various previous investigations demonstrated that in situations with increased oxidative stress and endothelial dysfunction (HF, hypertension, high oxygen tension, and high salt status), the pronounced production of ROS initiated by aldosterone is likely to have detrimental effects on vascular function, resulting in further CV damage.[37]

Limitations and strengths

Our sample was composed of elderly Caucasians of European ancestry, so generalizations to other ethnicities and younger individuals cannot be made. The observational design of our study precludes conclusions with regard to causal relationships. Plasma sodium is definitely a worse indicator of dietary sodium intake than the 24 h urine sodium excretion, which was unfortunately not available. Aldosterone was measured only once at baseline,

and LVEF was determined in only 43% of the cohort. Finally, the relatively low number of fatal CVD events in distinct subgroups, however, may have limited our ability to detect statistically significant results. Despite these limitations, our study has several strengths, particularly the in-depth clinical and biochemical characterization of the patients. Multiple conventional risk factors representing key pathological pathways implicated in the pathogenesis of CVD were available for conjoint and comparative multivariable analysis. Finally, our results are strengthened by the high number of participants eligible for mortality analyses and a considerable number of deaths within a sufficiently long period of follow-up.

Conclusions

Our results indicate that aldosterone levels well within the physiological range might play an important role in the development of fatal CVD events and may thus provide a plausible explanation for the benefits obtained from MR blocking treatment in the RALES and EPHESUS trials. Furthermore, our findings may contribute to resolve the paradox of deleterious aldosterone-mediated effects in individuals with relative aldosterone excess in regard to inappropriate body salt status and call for further prospective and mechanistic trials to evaluate beneficial effects of blocking aldosterone function across a broad spectrum of CVD.

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CARDIOVASCULAR FLASHLIGHT

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Left to right protrusion of a left atrial myxoma through a patent foramen ovale in a patient with 'cryptogenic' pulmonary embolism

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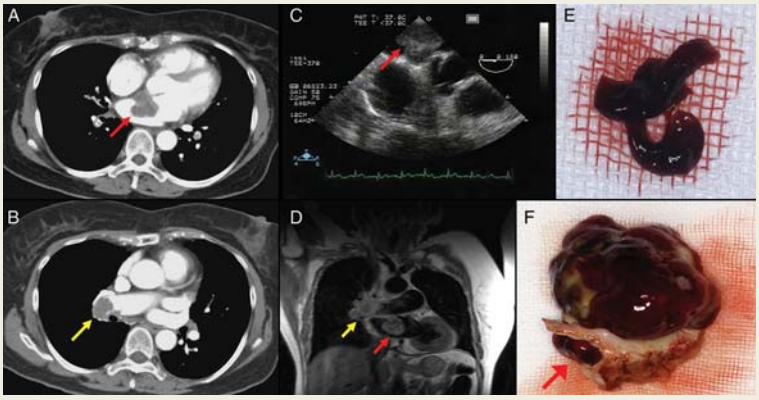

A 66-year-old woman had been well until 6 days earlier, when she experienced dyspnoea. Because of hypoxaemia and inverted T waves in the right precordial leads, pulmonary thrombo-embolus was suspected, although she had no remarkable coagulation factor abnormality, including antiphospholipid antibodies. A contrast-enhanced computed tomography showed that an embolic fragment was occluding the right pulmonary main artery (RPMA) without any lower limb venous thrombus (*Panel B*). Unexpectedly, a left atrium (LA) mass (3.2 × 2.4 cm) was demonstrated simultaneously (*Panel A*). A transoesophageal echocardiographic study revealed that the mass was pedunculated and originated from the base of interatrial septum, indicating LA myxoma (*Panel C*). Further detailed echocardiographic examination revealed that the mass protruded into the right atrium (RA), apparently through a patent foramen ovale (PFO) (see Supplementary material online, *Movie S1*). In this case, pulmonary embolism could have been associated with the protruded mass. However, this possibility might be difficult to diagnose with certainly pre-operatively, even with magnetic resonance imaging (*Panel D*). The operation was performed under a standard cardiopulmonary bypass. The excised mass was originated from the interatrial base and traversed the septum into RA, apparently through a PFO (*Panel F*), and two thrombi were removed from RPMA (*Panel E*). An LA myxoma and pulmonary thrombi without tumour were confirmed by histopathological study. There is increasing evidence that cardiac myxomas constitutively secrete a variety of growth factors and cytokines and they could have a role in the thrombosis on the myxoma surface and systemic embolisms, although myxoma *per se* has been implicated as an embolic source.

Supplementary material

Supplementary material is available at *European Heart Journal* online.