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Soluble Urokinase Plasminogen Activator Receptor (suPAR) as A Predictor of Incident Atrial Fibrillation

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Abstract

Soluble urokinase plasminogen activator receptor (suPAR) is a biomarker of chronic low-grade inflammation and a potent predictor of cardiovascular events. We hypothesized that plasma suPAR levels would predict new-onset atrial fibrillation (AF) in a large cohort of consecutively admitted acute medical patients during long-term follow-up. In 14,764 acutely ad-mitted patients without prior or current AF, median suPAR measured upon admission was 2.7 ng/ml (interquartile range (IQR) 1.9-4.0). During a median follow-up of 392 days (IQR 218–577), 349 patients (2.4%) were diagnosed with incident AF.

suPAR levels at admission significantly predicted subsequent incident AF (HR per doubling of suPAR: 1.21, 95% CI 1.05-1.41, adjusted for age and sex). After further adjustment for Charlson score, plasma C-reactive protein (CRP), plasma creatinine and blood hemoglobin-levels, the result remained essentially unaltered (HR per doubling of suPAR: 1.20, 95% CI: 1.01-1.42). In multivariate ROC curve analysis, combining age, sex, Charlson score, CRP, creatinine, and hemoglobin (AUC 0.77, 95% CI 0.75-0.79), the addition of suPAR did not improve the prediction of incident AF (AUC 0.77, 95% CI 0.75-0.79, P=0.89).

Plasma suPAR is independently associated with subsequent new-onset AF in a population of recently hospitalized patients, but the addition of suPAR to baseline risk markers appears not to improve the prediction of AF.

Introduction

Atrial fibrillation (AF) is a frequently seen cardiac rhythm disturbance, especially among el-derly patients. In 2010, global estimates of AF prevalence reached 596.2 per 100,000 in men and 373.1 per 100,000 in women[1]. The clinical manifestations of AF span the diorama from asymptomatic affliction, to patients suffering severe hemodynamic consequences and related complications, such as acute progression of congestive heart failure, ischemic stroke, as well as markedly reduced survival[2],[3]. Alterations in the normal physiology of the atria, mediated by metabolic or structural changes, can incite AF [4]. Inflammation and oxidative stress may be linked to the development of AF[5]. Elevation of inflammatory markers, such as plasma C-reactive protein (CRP) and inter-leukin-6, have been shown to predict development of AF[6]. suPAR is the soluble form of the membrane-bound urokinase plasminogen activator receptor (uPAR). Upon activation, urokinase converts plasminogen into plasmin, thus triggering a pro-teolytic cascade participating in thrombosis or degradation of the extracellular matrix, de-pending on the environment. suPAR concentration in blood/plasma/serum correlates to the level of activation of the immune system. As a novel biomarker of chronic low-grade inflam-mation, suPAR is related to a myriad of medical conditions, and it has been shown to surpass CRP and other traditional inflammation markers in predicting cardiovascular disease (CVD)[7]. This may be due to suPAR being more tightly related to subclinical cardiovascular dam-age[7],[8]. Furthermore, unlike other inflammatory markers, suPAR levels remain unchanged during acute cardiac events and suPAR is in this sense not considered an acute phase reactant[7],[9]. In this study, we aimed to investigate whether suPAR was predictive of incident AF in acutely admitted medical patients with no prior history of AF.

Key Words

suPAR, Predictor, Atrial fibrillation, Soluble Urokinase Plasminogen Activator Receptor

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Methods

Setting and study design

The study was a registry-based cohort study of patients admitted to the Acute Medical Unit (AMU), Copenhagen University Hospital Hvidovre, Capital Region, Denmark, between No-vember 18, 2013, and September 30, 2015. Patients were included if they had plasma suPAR levels measured as part of the standard ad-mission blood tests. Patients with a prior or current diagnosis of AF (International Classifica-tion of Diseases-10th Revision (ICD-10) I48) at the time of the index admission were exclud-ed from further analysis. The remaining patients were followed until December 31st 2015. su-PAR data on a subgroup of this cohort has previously been published[10]. The index admission was defined as the first admission where a patient had his or her suPAR level measured. Information on admissions and diagnoses was obtained via the Danish Na-tional Patient Registry (NPR), where all contacts with the secondary health care system are registered. Contacts for hospital admissions less than five hours apart were considered coher-ent and coded as the same admission.

Prevalent co-morbidity at the index admission was defined as diagnoses of interest registered before or during the index admission.

These included ICD-10 codes for diabetes (E10-E14), hypertension (I10–I15), congestive heart failure (I099, I110, I130, I132, I255, I420, I425–I429, I43, I50), stroke (I60-I64, G459), embolism (H341A, I740B, I741A, I742A, I743A, I744A, I744C, I745A, I803A, N280A), and vascular disease (I20-I25, I70, I71, I731, I738, I739, I771, I790, I792, K551, Z958, Z959). Furthermore, the Charlson comorbidity index was calculated for each patient based on the patient's comorbid conditions as previously described[11]. Briefly, the score is calculated based on a weighted scoring system where severe and multiple comorbidities increase the cumulative score[12], using the updated weighting[13].

During follow-up, information on incident AF and vital status was obtained from the NPR and the Danish Civil registration System, respectively.

Measurement of biomarkers

Blood samples were analyzed at the Department of Clinical Biochemistry and results were extracted from the electronic hospital database LABKA. Plasma suPAR levels were deter-mined in singlets using the suPARnostic AUTO Flex ELISA kit on an automated Siemens BEP2000 platform according to the manufacturer's instructions (ViroGates A/S, Birkerød, Denmark). The fresh plasma samples were analyzed in batches once daily during weekdays (within 0–72 hours after blood sampling). The assay had a precision (coefficient of variation) of 5.1% at 2 ng/mL and 1.7% at 7 ng/mL. Plasma CRP and creatinine were analyzed using a COBAS 6000 analyzer (Roche Diagnos-tics, Mannheim, Germany). Hemoglobin was analyzed using a Sysmex XN 9000.

Statistical Analysis

Continuous variables are described by median and interquartile range (IQR), and categorical variables are described by number (n) and percentages (%). Differences between groups were tested with Wilcoxon or chi-square test where appropriate.
Adjusted Cox regression analyses were performed to estimate the effect of suPAR on AF. Ad-justments were made for age and sex, and further adjustments were made for Charlson score, CRP, creatinine, and hemoglobin. In the Cox models, suPAR was used as a continuous varia-ble (log2-transformed) or as a categorical variable stratified in tertiles. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). SAS Enterprise Guide 7.11 (SAS Institute) and R 3.2.3 (The R Foundation for Statistical Computing) were used for statistical analysis. A P value <0.05 was considered to be statistically significant.

Results

During the inclusion period, 20,193 samples were ordered. suPAR was analyzed in 18,009 cases. After exclusions due to invalid civil registration number (n=505), loss to follow-up (n=109), missing NPR data (n=40), suPAR below the assay range (<0.5 ng/ml, n=43), and prevalent AF (n=2,548), the final population comprised 14,764 patients. Baseline characteris-tics of the population are shown in [Table 1].

The ten most frequent index admission diagnoses for the entire population are shown in [Table 2], with the corresponding frequencies for the subpopulation with subsequent AF.

During a median follow-up of 392 days (IQR 218–577), incident AF was diagnosed in 349 patients (2.4%) during follow-up. Patients with subsequently diagnosed AF differed signifi-cantly from the overall population on several baseline parameters, as outlined in [Table 1], in-cluding higher age, more chronic diagnoses, lower blood hemoglobin, and higher plasma lev-els of CRP, creatinine, and suPAR.

Continuous suPAR and risk of incident AF

When adjusted for age and sex, the HR of incident AF per doubling of plasma suPAR was 1.21 (95% CI: 1.05-1.41, P = 0.01), meaning that for every doubling of suPAR, the risk of incident AF increased by 20%. This result remained essentially unaltered after further adjust-ment for Charlson score, CRP, creatinine, and hemoglobin (HR per

Table 1: Baseline characteristics of acutely admitted patients without prior or current atrial fibrillation (AF)

	All patients (n=14,764)	Patients with no subsequent AF (n=14,415)	Patients with subsequent atrial fibrillation (n=349)	P
Male,n(%)	6,801 (46.1)	6,639 (46.1)	162 (46.4)	0.89
Age (years), median (IQR)	57.5 (40.1–73.1)	56.9 (39.7–72.5)	76.6 (68.0–84.7)	<0.0001
Length of index admission (days), median (IQR)	0.76(0.30–2.92)	0.75 (0.30–2.87)	1.3 (0.5–5.5)	<0.0001
Comorbidities*:				
Diabetes, n (%)	2,054 (13.9)	1,989 (13.8)	65 (18.6)	<0.0001
Arterial hypertension, n (%)	4,037 (27.3)	3,852 (26.7)	185 (53.0)	<0.0001
Congestive heart failure, n (%)	1,051 (7.1)	974 (6.8)	77 (22.1)	<0.0001
Previous stroke/TCI/emboli, n (%)	1,713 (11.6)	1,651 (11.5)	62 (17.8)	<0.0001
Vascular disease, n (%)	3,162 (21.4)	3,035 (21.1)	127 (36.4)	<0.0001
Charlson score (median, IQR)	0 (0–1)	0 (0–1)	0 (0–2)	<0.0001
Biomarkers, median (IQR):				
Plasma suPAR (ng/ml)	2.7 (1.9–4.0)	2.6 (1.9–3.9)	3.6 (2.6–5.2)	<0.0001
Plasma CRP (mg/l)	5 (1–29)	5 (1–29)	8 (2–44)	<0.0001
Plasma creatinine (ng/ml)	72 (60–89)	72 (60–89)	82 (64–105)	<0.0001
Blood hemoglobin (mmol/l)	8.3 (7.5–9.0)	8.3 (7.5–9.0)	7.9 (7.2–8.6)	<0.0001

* International Classification of Diseases-10th Revision (ICD-10) diagnoses: Diabetes: E10-E14. Arterial hypertension: I10–I15. Congestive heart failure: I099, I110, I130, I132, I255, I420, I425–I429, I43, and I50. Stroke: I60-I64 and G459. Emboli: H341A, I740B, I741A, I742A, I743A, I744A, I744C, I745A, I803A, N280A. Vascular disease: I20-I25, I70, I71, I731, I738, I739, I771, I790, I792, K551, Z958, and Z959. IQR: Interquartile range. SD: Standard deviation. TCI: Transitory cerebral ischemia.

doubling of suPAR: 1.20, 95% CI: 1.01-1.42, P = 0.037).
In multi variate receiver operating characteristic (ROC) analysis to predict AF, the area under the curve (AUC) for the combination of age, sex, Charlson score, CRP, creatinine, and hemoglobin was 0.77 (95% CI: 0.75-0.79). The addition of suPAR to the model did not change this result (P = 0.66).

suPAR tertiles and risk of incident AF

When dividing suPAR levels in tertiles, we found a significantly increased risk of incident AF in patients with a baseline suPAR in the highest tertile compared to the lowest tertile after controlling for age and sex (HR: 1.42, 95% CI: 1.02–1.97, P = 0.039). After further adjust-ment for Charlson score, CRP, creatinine, and hemoglobin, the result was attenuated (HR: 1.30, 95% CI: 0.92–1.86, P = 0.14).

Discussion

We present data demonstrating a significant, yet modest, correlation between baseline suPAR levels and subsequent incident AF in a large and diverse population of patients seeking emer-gency care, due to medical conditions unrelated to AF. After multivariate adjustment, a dou-bling of suPAR corresponded to a 20% increase in risk of incident AF.

To our knowledge, the relationship between suPAR and incident AF has been investigated in only one prior study. In 2014, Borné and colleagues reported a positive association between suPAR and incident AF among subjects participating in the Malmö Cancer and Diet study during 1991-1996, but after adjustment for conventional risk factors and biomarkers, the cor-relation was not significant[14]. The studies differ on several issues. Primarily, we studied a population of recently admitted patients, whereas Borné and colleagues studied a general population sample from the Malmö Diet and Cancer Study. Furthermore, the observation time in the Swedish study was much longer (mean follow-up 16.3 years) than our median follow-up of 392 days. This large difference in time from baseline to endpoint might explain the different results.

Table 2: 10 most frequent diagnoses during the index admission for acutely admitted patients without prior or current atrial fibrillation (AF)

	All patients (n=14,764)	Patients with subsequent atrial fibrillation (n=349)
1: Z034, n (%)	1097 (7.4)	22 (6.3)
Observation for acute myocardial in-farction		
2: J189, n (%) Pneumonia	619 (4.2)	30 (8.6)
3: Z038, n (%) Observation for unspecified condition	581 (3.9)	7 (2.0)
4: R074, n (%) Chest pain, unspecifiedChest painunspecified	446 (3.0)	6 (1.7)
5: J960, n (%) Acute respiratory failure	368 (2.5)	17 (4.9)
6: Z035, n (%) Observation for other cardiovascular condition	302 (2.0)	5 (1.4)
7: I109, n (%) Arterial hypertension	263 (1.8)	6 (1.7)
8: J459, n (%) Asthma	257 (1.7)	3 (0.9)
9: F100, n (%) Alcohol intoxication	243 (1.6)	1 (0.3)
10: R429, n (%) Vertigo	231 (1.6)	4 (1.1)

Recently, a Japanese study showed an association between prevalent AF, especially non-paroxysmal AF, and increasing suPAR levels, although the association lost significance in multivariate models[15]. The relationship between inflammation and risk of cardiovascular disease is well documented[6,16,17] and it is broadly confirmed that inflammation contributes to the pathophysiology of AF[18-21]. Hence, inflammation seems to play an important role in the development of AF as well as in the pathogenesis of cardiovascular diseases related to incident AF. Especial-ly, CRP has been shown to correlate with increased risk of new onset and recurrent AF[22-24].

Although suPAR and CRP are correlated and both are related to lifestyle risk factors, such as smoking and low physical activity, suPAR and CRP are quite different from each other with respect to their correlation to subclinical organ damage and metabolic relationships and seem to belong to different pathways[7]. Notably, suPAR seems to be more closely related to endothelial dysfunction, which is meticulously associated with AF[25]. Furthermore, in contrast to CRP and other traditional markers of inflammation, suPAR remains unchanged after a major surgical procedure such as coronary artery bypass graft (CABG) and in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary interven-tion[26,27]. Here, we found a significant correlation between suPAR and incident AF after adjustment for plasma CRP. Although we found a significant association between suPAR and incident AF, the correlation was of modest proportion. Furthermore, when dividing suPAR levels into tertiles, the correla-tion was no longer statistically significant after multivariate adjustment, and in ROC curve analysis, the addition of suPAR (as a continuous variable) to conventional baseline risk mark-ers did not improve the prediction of incident AF during follow-up. Whether suPAR has a po-tential role in future schemes of prediction of AF is uncertain. Our data do not support the clinical use of suPAR for this specific purpose, but further investigation is warranted with re-spect to size and selection of population sample.

Strengths and Weaknesses

We included data from a large sample of acutely admitted patients. The NPR allows near complete follow-up for incident AF. The validity of data from the NPR is generally high in-cluding the diagnosis AF and other cardiovascular diagnoses[28-30].

We cannot exclude the risk of potential underreporting of atrial fibrillation at index admission or during follow up, but we have no reason to believe that this would result in a systematic bias.

Since our study included patients admitted in our Acute Medical Unit, the adjustment for CRP was of particular importance. This was done in order to reduce the risk of indication bias, i.e. that the condition for which the patients were admitted was associated with increased CRP and risk of AF rather than suPAR. To reduce the risk of bias further, we performed separate sensitivity analyses, omitting data from patients with incident AF within 30 days from base-line. The results of these analyses were essentially no different from the main results (data not shown).

The nature of our study does not allow us to imply a causal relationship between suPAR and incident AF. In fact, the specific role of inflammation in AF is yet imprecisely defined and the clinical

relevance of raised inflammatory markers as a correlate to AF is elusive.

Conclusion

We found a significant correlation between suPAR and subsequent risk of AF in a large popu-lation of patients seeking emergency care, due to medical conditions unrelated to AF. After multivariate adjustment, a doubling of suPAR corresponded to a 20% increase in risk of incident AF.

However, the addition of suPAR to conventional baseline risk markers did not improve the prediction of incident AF. Further research is warranted in order to define the role of inflam-mation and inflammatory markers - including suPAR - in AF.

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