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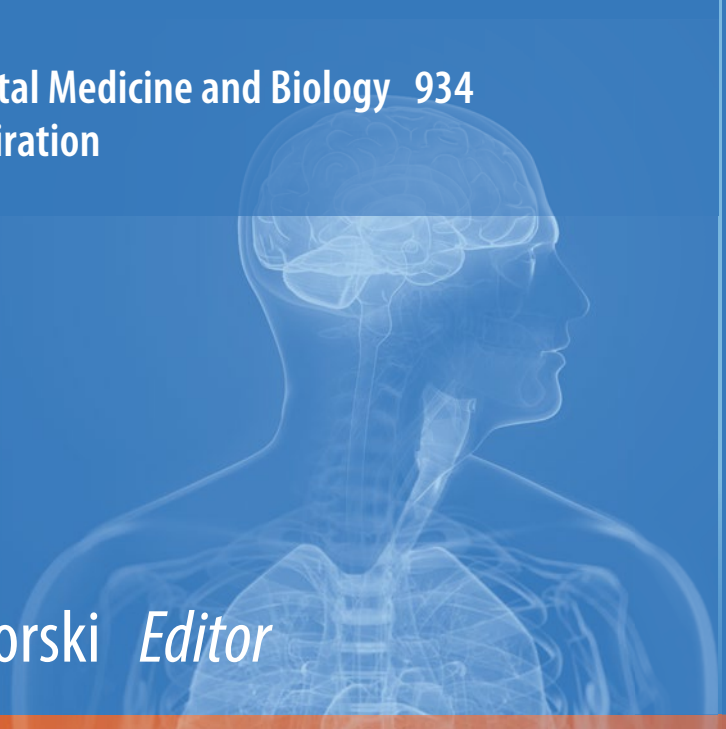
Neuroscience and Respiration



Mieczyslaw Pokorski *Editor*

Pulmonary Dysfunction and Disease

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Editor

Pulmonary Dysfunction and Disease

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Preface

The book series *Neuroscience and Respiration* presents contributions by expert researchers and clinicians in the field of pulmonary disorders. The chapters provide timely overviews of contentious issues or recent advances in the diagnosis, classification, and treatment of the entire range of pulmonary disorders, both acute and chronic. The texts are thought as a merger of basic and clinical research dealing with respiratory medicine, neural and chemical regulation of respiration, and the interactive relationship between respiration and other neurobiological systems such as cardiovascular function or the mind-to-body connection. The authors focus on the leading-edge therapeutic concepts, methodologies, and innovative treatments. Pharmacotherapy is always in the focus of respiratory research. The action and pharmacology of existing drugs and the development and evaluation of new agents are the heady area of research. Practical, data-driven options to manage patients will be considered. New research is presented regarding older drugs, performed from a modern perspective or from a different pharmacotherapeutic angle. The introduction of new drugs and treatment approaches in both adults and children also is discussed.

Lung ventilation is ultimately driven by the brain. However, neuropsychological aspects of respiratory disorders are still mostly a matter of conjecture. After decades of misunderstanding and neglect, emotions have been rediscovered as a powerful modifier or even the probable cause of various somatic disorders. Today, the link between stress and respiratory health is undeniable. Scientists accept a powerful psychological connection that can directly affect our quality of life and health span. Psychological approaches, by decreasing stress, can play a major role in the development and therapy of respiratory diseases.

Neuromolecular aspects relating to gene polymorphism and epigenesis, involving both heritable changes in the nucleotide sequence and functionally relevant changes to the genome that do not involve a change in the nucleotide sequence, leading to respiratory disorders will also be tackled. Clinical advances stemming from molecular and biochemical research are but possible if the research findings are translated into diagnostic tools, therapeutic procedures, and education, effectively reaching physicians and patients. All that cannot be achieved without a multidisciplinary, collaborative, bench-to-bedside approach involving both researchers and clinicians.

The societal and economic burden of respiratory ailments has been on the rise worldwide leading to disabilities and shortening of life span. COPD alone causes more than three million deaths globally each year. Concerted efforts are required to improve this situation, and part of those efforts are gaining insights into the underlying mechanisms of disease and staying abreast with the latest developments in diagnosis and treatment regimens. It is hoped that the books published in this series will assume a leading role in the field of respiratory medicine and research and will become a source of reference and inspiration for future research ideas.

I would like to express my deep gratitude to Mr. Martijn Roelandse and Ms. Tanja Koppejan from Springer's Life Sciences Department for their genuine interest in making this scientific endeavor come through and in the expert management of the production of this novel book series.

Opole, Poland Mieczyslaw Pokorski

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Adiponectin and Mortality in Smokers and Non-Smokers of the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study

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Abstract

Cardiovascular diseases (CVD) are an important cause of morbidity and mortality worldwide. A decreased concentration of adiponectin has been reported in smokers. The aim of this study was to analyze the effect of cigarette smoking on the concentration of adiponectin and potassium in active smokers (AS) and life-time non-smokers (NS) of the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study, and the use of these two markers for risk prediction. Smoking status was assessed by a questionnaire and measurement of plasma cotinine concentration. The serum concentration of adiponectin was measured by ELISA. Adiponectin was binned into tertiles separately for AS and NS and the Cox regression was used to assess the effect on mortality. There were 777 AS and 1178 NS among the LURIC patients. Within 10 years (median) of follow-up 221 AS and 302 NS died. In unadjusted analyses, AS had lower

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concentrations of adiponectin. However, after adjustment for age and gender there was no significant difference in adiponectin concentration between AS and NS. In the Cox regression model adjusted for age and gender, adiponectin was significantly associated with mortality in AS, but not in NS, with hazard ratio (95 % CI) of 1.60 (1.14–2.24) comparing the third with first tertile. In a model further adjusted for the risk factors, such as diabetes mellitus, hypertension, coronary artery disease, body mass index, LDL-cholesterol and HDL-cholesterol, adiponectin was significantly associated with mortality with hazard ratio of 1.83 (1.28–2.62) and 1.56 (1.15–2.11) for AS and NS, respectively. We conclude that increased adiponectin is a strong and independent predictor of mortality in both AS and NS. The determination of adiponectin concentration could be used to identify individuals at increased mortality risk.

Keywords
Adipokines • Biochemical markers • Cardiovascular disease • Smoking • Mortality • Risk factors

1 Introduction

Cigarette smoking is an addictive habit that has influenced the behavior of people for more than four centuries. Worldwide, reductions in the estimated prevalence of daily smoking have been observed since 1980, but because of the population growth, the absolute number of active smokers has increased from 721 million in 1980 to 967 million in 2012 (Ng et al. 2014). Further, it was estimated in 2004 that 40 % of children, 33 % of male non-smokers, and 35 % of female non-smokers are exposed to second-hand smoke (Oberg et al. 2011). Tobacco continues to be a major cause of death, leading to 5.7 million deaths, 6.9 % of years of life lost, and 5.5 % of disability adjusted life-years (DALYs) (Lim et al. 2012).

A number of different mechanisms of action have been proposed that mediate the deleterious effects of cigarette smoking, e.g., increased inflammation, increased risk for thrombosis, or oxidative stress (Ambrose and Barua 2004). In recent years, it has been reported that smokers show decreased concentrations of adiponectin in plasma and tissues (Li et al. 2015; Iwashima et al. 2005) *In vitro* experiments have demonstrated that nicotine significantly decreases adiponectin secretion by adipocytes, in part through altering ATP-sensitive potassium channels (Fan et al. 2015).

Adiponectin is secreted by both white and brown adipose tissue and circulates in blood in multimeric forms, such as trimeric, hexameric, and high molecular mass species (Chakraborti 2015). It has been extensively studied because of its insulin sensitizing and antiatherogenic properties. Unlike other adipokines, adiponectin circulating concentration is decreased not only in smokers but also in the obese or type 2 diabetics. Physiological functions of adiponectin are the following: stimulation of fatty acid (FA) oxidation, reduction of lipid accumulation in muscles, reduction of plasma FA concentration, and the improvement of insulin sensitivity. Further, adiponectin inhibits macrophage activation and foam cell accumulation, and increases endothelial nitric oxide (NO) production with a reduction in platelet aggregation (Shehzad et al. 2012). Therefore, adiponectin may protect against coronary heart disease (CHD), steatohepatitis, and non-alcoholic fatty liver disease. On the other hand, no association of adiponectin with CHD progression has been found, but meta-analyses

have shown an association with increased mortality (Wu et al. 2014; Sook Lee et al. 2013).

The aim of this study was to examine the association of adiponectin with mortality in active smokers (AS) and life-time non-smokers (NS) with a medium-to-high risk of coronary events.

2 Methods

2.1 Study Population

The study was approved by the 'Landesärztekammer' Ethics Committee of the Rheinland-Pfalz state in Germany and all patients gave written consent at study entry. The LUdwigshafen RIsk and Cardiovascular Health (LURIC) study has been an ongoing prospective study of 3316 patients of German ancestry who had an indication for coronary angiography. Patients were recruited between June 1997 and May 2001 at the Ludwigshafen Cardiac Center (Winkelmann et al. 2001). All patients were clinically stable, except for acute coronary syndromes. Information on vital status was obtained from local registries. Death certificates were obtained in 97 % of dead participants. Only were AS and life-time NS included into analysis. In both groups, there occurred 523 deaths (26.8 %) during a median follow-up of 10 years. Smoking status was assessed based on a questionnaire and verified by the measurement of serum cotinine concentration.

2.2 Laboratory Procedures

Fasting blood samples were taken by venipuncture in the early morning prior to angiography. Aliquots were frozen at −80 °C. Cholesterol and triglycerides were measured with enzymatic reagents from WAKO (Neuss, Germany) on an Olympus AU640 analyser (Center Valley, PA). Adiponectin serum concentration were measured by ELISA (Biovendor Laboratory Medicine, Brno, Czech Republic). Galectin-3 concentration was measured on an ARCHITECT analyzer (Abbott Diagnostics, Abbott Park, IL). hsCRP was determined by immunonephelometry on a Behring Nephelometer II (N High Sensitivity CRP, Dade Behring, Germany).

2.3 Statistical Analyses

All continuous variables were checked for normality and variables showing a skewed distribution were logarithmically transformed to get a normal distribution. Continuous variables were compared between groups by Student's *t*-test. Associations between categorical variables were examined by chi-squared testing. To examine the relationship of adiponectin with mortality, we split AS and NS into tertiles according to adiponectin concentration and calculated hazard ratios (HR) and 95 % confidence intervals (95 % CI) using the Cox proportional hazards model. Multivariable adjustment was carried out as indicated. IBM SPSS Statistics v. 21.0 and R statistical software v. 3.2.2 (http://www.r-project.org) were used for all analyses.

3 Results

Among the LURIC patients, there were 777 AS and 1178 life-time NS. The proportion of men was higher in the AS group and AS were younger as compared to NS (Table 1). LDL-C and HDL-C were lower in AS but the concentrations of oxidized LDL and triglycerides were higher as compared to NS. Systemic inflammation, as measured by the concentration of hsCRP, was higher in AS, but there was no difference in the concentration of galectin-3, a marker of fibrosis. AS had a higher mean estimated glomerular filtration rate (eGFR) and a lower percentage of hypertension, but there was a higher percentage of patients suffering from coronary artery disease and a higher proportion of patients treated with lipid lowering drugs (mostly statins) in the AS group as compared to life-time non-smokers. In unadjusted analyses, AS had lower concentrations of adiponectin. However,

Table 1 Anthropometric characteristics of patients at study onset

	Never smokers (*n = 1178*)	Active smokers (*n = 777*)	p
Age (yr)	65.3 ± 10.1	56.2 ± 10.3	<0.001
Male sex (%)	45.4	77.9	<0.001
BMI (kg/m^2)	27.4 ± 4.2	27.0 ± 4.2	0.833
LDL-C (mg/dl)	119.1 ± 36.4	117.5 ± 32.1	0.012
Oxidized LDL-C (U/l)	73.5 ± 26.7	78.4 ± 25.4	<0.001
HDL-C (mg/dl)	41.2 ± 11.1	36.2 ± 10.2	0.002
Triglycerides (mg/dl)	136 (102–192)	154 (112–218)	<0.001
Galectin-3 (ng/ml)	15.8 ± 6.3	15.5 ± 7.3	0.496
hsCRP (mg/l)	2.72 (1.17–7.04)	4.93 (1.84–10.30)	<0.001
eGFR (ml/min/1.73 m^2)	78.7 ± 19.1	88.2 ± 20.1	<0.001
Adiponectin (μg/ml)	9.7 (6.4–14.8)	7.6 (5.2–11.7)	<0.001
Adjusted adiponectin* (μg/ml)	11.4 (10.6–12.3)	11.2 (10.1–12.3)	0.345
Coronary artery disease (%)	68.1	80.1	<0.001
Diabetes mellitus (%)	38.3	36.0	0.314
Hypertension (%)	76.6	63.3	<0.001
Lipid lowering therapy (%)	42.4	52.8	<0.001

Data are means ± SD or median and 25–75th percentile
BMI body mass index, *eGFR* estimated glomerular filtration rate, *HDL-C* high density lipoprotein cholesterol, *hsCRP* high sensitive C-reactive protein, *LDL-C* low density lipoprotein cholesterol
*Estimated marginal means (95 % CI) adjusted for age and gender

Table 2 Adiponectin concentration in never smokers and active smokers stratified for gender

	Never smokers		Active smokers		
	n	Median (25th–75th percentile)	n	Median (25th–75th percentile)	p
Males					
Adiponectin (μg/ml)	520	7.9 (5.4–11.6)	582	6.8 (4.7–10.3)	<0.001
Females					
Adiponectin (μg/ml)	618	11.6 (7.9–17.0)	167	10.8 (7.6–15.1)	0.312

after adjustment for age and gender, there was no significant difference in adiponectin concentration anymore. In gender stratified analyses, adiponectin was significantly higher in females than in males and only for males there was a significant difference comparing NS and AS (Table 2).

In the Cox regression model adjusted for age and gender, adiponectin was significantly associated with mortality only in AS with a hazard ratio of 1.60 (95 % CI 1.14–2.24) comparing the 3rd with 1st tertile (Table 3 and Fig. 1). In a model additionally adjusted for the risk factors diabetes mellitus, hypertension, coronary artery disease, BMI, LDL-C, and HDL-C adiponectin was significantly associated with mortality with HR of 1.83 (1.28–2.62) and 1.56 (1.15–2.11) for AS and NS, respectively. Hazard ratio plots modeling adiponectin as restricted cubic spline show an approximately linear association of adiponectin concentration with risk in females while in males there was a steeper risk increase below an adiponectin concentration of 10 μg/ml, and almost three fourth of all men presented with adiponectin concentrations in this range (Fig. 2).

4 Discussion

The major finding of this study is that adiponectin was a strong and independent predictor of mortality for both life-time non-smokers and active smokers in a cohort of patients referred

Table 3 Cox regression analysis of tertiles of adiponectin and all-cause mortality

		Never smokers			Active smokers	
	n	HR (95 % CI)	p	n	HR (95 % CI)	p
Model 1						
1st tertile	380	1		250	1	
2nd tertile	380	0.89 (0.66–1.20)	0.458	251	0.96 (0.67–1.37)	0.802
3rd tertile	378	1.10 (0.83–1.47)	0.501	248	1.60 (1.14–2.24)	0.006
P_{trend}			0.348			0.003
Model 2						
1st tertile	380	1		249	1	
2nd tertile	380	1.10 (0.81–1.49)	0.535	251	1.04 (0.72–1.51)	0.821
3rd tertile	378	1.56 (1.15–2.11)	0.004	248	1.83 (1.28–2.62)	0.001
P_{trend}			0.009			0.001

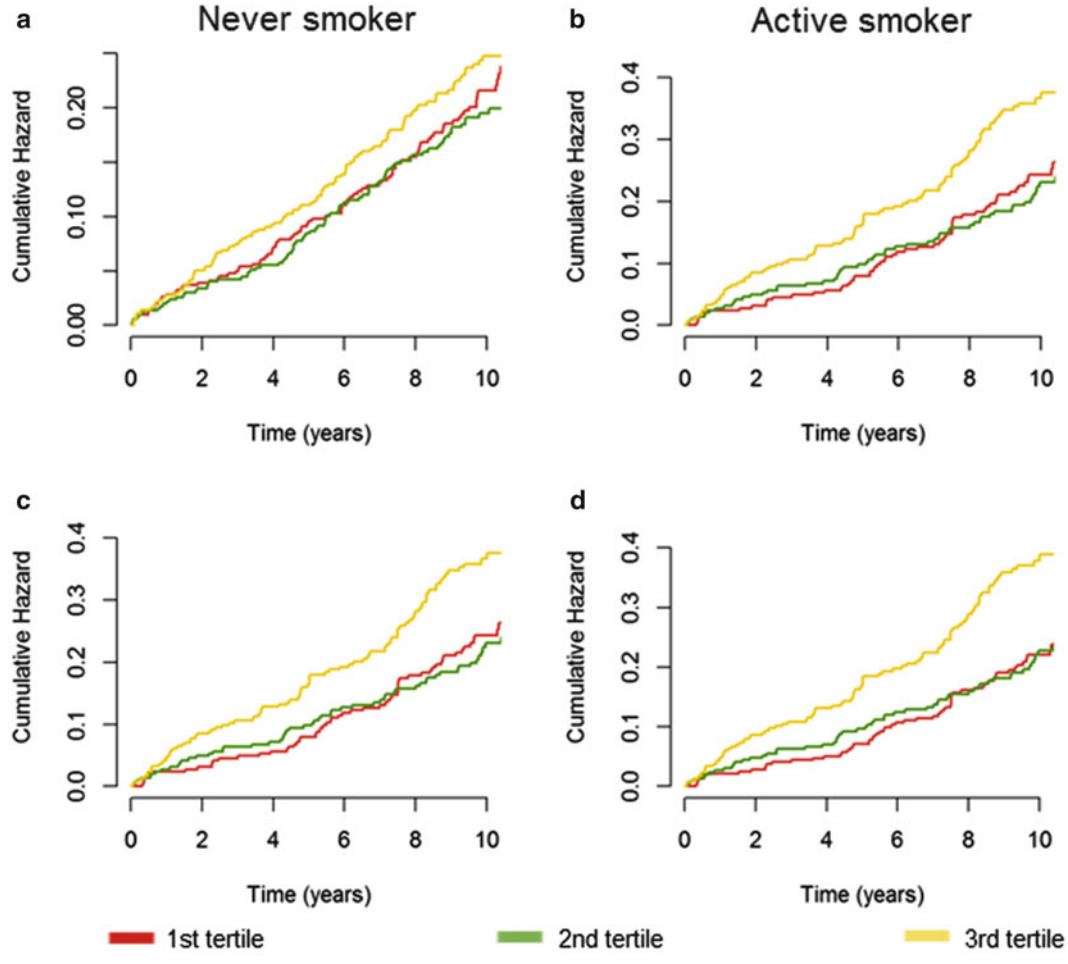

Fig. 1 Cumulative hazard curves showing tertiles of adiponectin for never-smokers (A + C) and active smokers (B + D). The two graphs in the upper row (A + B) show analyses adjusted for age and gender, the two graphs in the lower row (C + D) show analyses additionally adjusted for diabetes mellitus, hypertension, coronary artery disease, BMI, LDL-C, and HDL-C

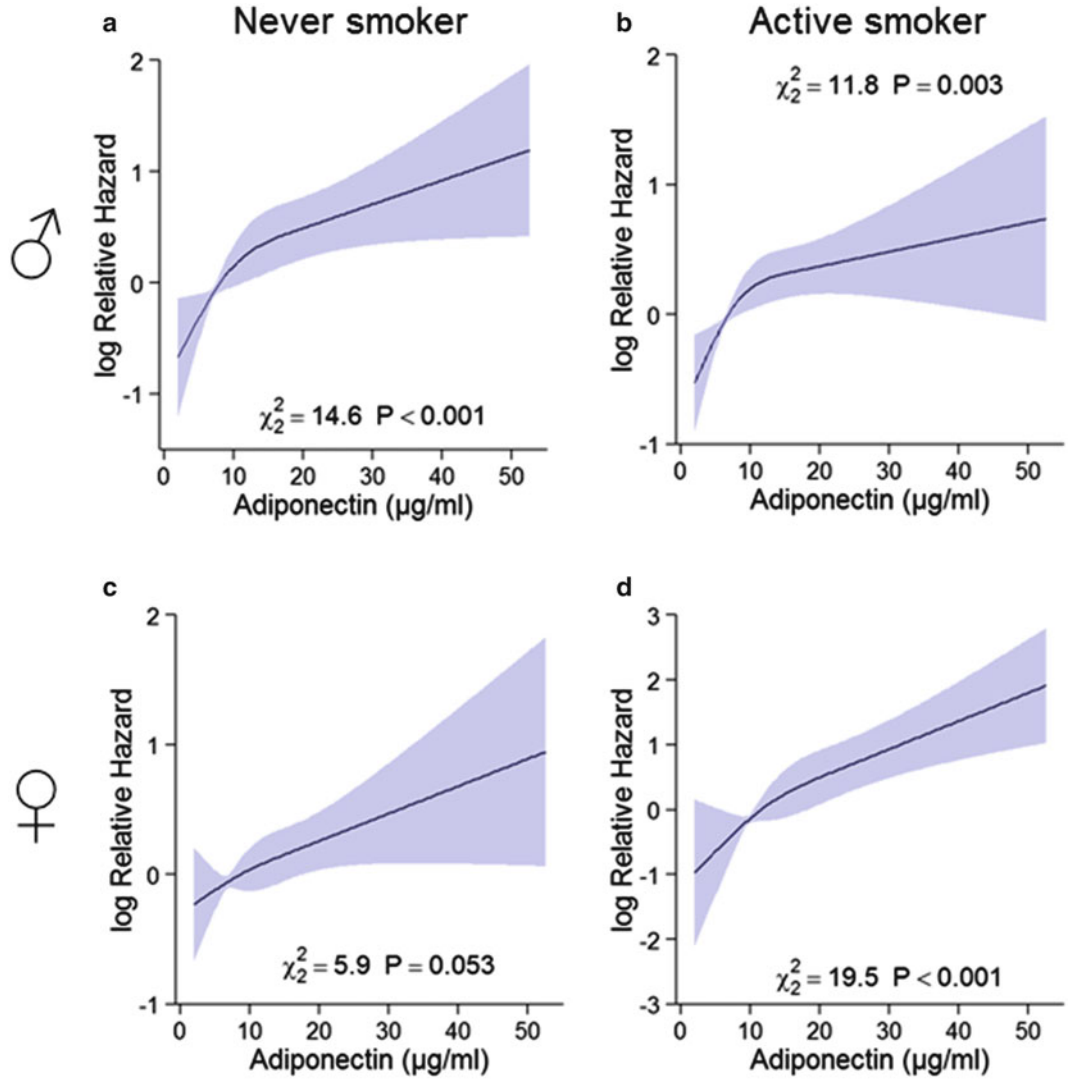

Fig. 2 Hazard ratio plots showing the association of adiponectin with all-cause mortality stratified by gender in never-smokers and active smokers

for coronary angiography. Adipocytes secret a variety of so called adipokines that are involved in the regulation of many physiological processes in the body, like the metabolism of lipids and carbohydrates, haemostasis, or inflammation. The concentration of most adipokines increases with increasing adipocyte number, except for adiponectin whose concentration decreases with obesity (Hajer et al. 2008). A decreased concentration of adiponectin has also been reported in type 2 diabetics, patients with CHD, or smokers (Kotani et al. 2012).

Although adiponectin is associated with mostly beneficial metabolic effects, like insulin sensitization, higher lipid oxidation, and less inflammation, no association with the incidence of CHD has been found (Kanhai et al. 2013). Worse, adiponectin has been shown to correlate directly with mortality, especially in CHD patients (Wu et al. 2014; Sook Lee et al. 2013). In line with this, Pilz et al. (2006) have reported a low adiponectin serum concentration in LURIC participants with CHD, but found no association with CHD progression. In the present

study we set out to compare adiponectin concentration in AS and NS and to investigate its association with 10-year mortality. After adjustment for age and gender we found no significant difference in adiponectin concentration between AS and NS. In the Cox regression model using the same adjustment adiponectin was significantly associated with mortality only in AS, but not in NS. After further adjustment for traditional risk factors, adiponectin was significantly associated with mortality in both AS and NS. This difference for the never-smokers between both models is due mainly to the adjustment for diabetes and CHD. This seems plausible because both diseases are associated with lower adiponectin but higher mortality risk.

5 Limitations and Conclusions

All participants were of European ancestry and were recruited at a tertiary referral center. Therefore our findings may not be representative for a random population sample or applicable to other ethnicities. Furthermore, we only investigated active smokers and life-time non-smokers and excluded former smokers from the analyses. Adiponectin concentration has only been measured once at baseline. The major strength of the LURIC cohort is, however, the precise clinical and metabolic characterization of participants and its cross-sectional and prospective design.

We conclude that adiponectin is an independent risk factor for mortality in active smokers and life-time non-smokers after adjustment for coronary heart disease risk factors. In addition, adiponectin could be determined, as a potentially useful marker, for risk prediction in active smokers.

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Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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Heart Rate Variability and Arrhythmic Burden in Pulmonary Hypertension

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Abstract

A growing body of evidence indicates that sudden cardiac death constitutes a major cause of mortality in pulmonary hypertension (PH). As validated method to evaluate cardiac autonomic system dysfunction, alterations in heart rate variability (HRV) are predictive of arrhythmic events, particularly in left ventricular disease. Here, we sought to determine the clinical value of HRV assessment in PH. Sixty-four patients were allocated to different PH-subgroups in this prospectively conducted trial: 25 patients with pulmonary arterial hypertension (PAH), 11 patients with chronic thromboembolic PH (CTEPH), and 28 patients with COPD-induced PH. All patients underwent 24-h Holter electrocardiogram for HRV assessment by time- and frequency-domain analysis. Arrhythmic burden was evaluated by manual analysis and complementary automatic measurement of premature atrial and ventricular contractions. The results were compared to 31 healthy controls. The PAH patients offered a significantly higher mean heart rate (78.6 $\pm$ 10.4 bpm *vs.* 70.1 $\pm$ 10.3 bpm, $p = 0.04$), a higher burden of premature ventricular contractions ($p < 0.01$), and decreases in HRV (SDNN: $p < 0.01$; SDANN: $p < 0.01$; very low frequency: $p < 0.01$; low frequency/high frequency ratio: $p < 0.01$; total power: $p = 0.02$). In CTEPH patients, only the amount of premature ventricular contractions differed from controls ($p < 0.01$), whereas in COPD both premature atrial contraction count and frequency-domain-based HRV manifested significant differences.

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In conclusion, PAH appears to be primarily affected by HRV alterations and ventricular arrhythmic burden, indicating a high risk for malignant arrhythmic events.

Keywords
Atrial fibrillation • Echocardiography • Frequency-domain analysis • Right heart catheterization • Sudden cardiac death • Systolic pulmonary arterial pressure • Time-domain analysis

1 Introduction

Pulmonary hypertension represents a complex and heterogeneous disorder characterized by a multifactorial pathogenesis. In pulmonary arterial hypertension (PAH), proliferative pulmonary vasculopathy, triggered by vasoconstriction, fibrosis and thrombosis, induces vascular obliteration and elevation in pulmonary vascular resistance. In chronic thromoembolic pulmonary hypertension (CTEPH) and pulmonary hypertension due to lung disease, the underlying pathogenic mechanisms are less well defined. A common entity of the last-mentioned subgroup of pulmonary hypertension is chronic obstructive pulmonary disease (COPD) – caused PH, in which both hypoxia-induced vasoconstriction and obliteration of the vascular bed are the primary drivers of pulmonary vascular resistance increase (Seeger et al. 2013). The disease course is progressive, disabling, frequently fatal and highly dependent on the underlying type of pulmonary hypertension, with PAH offering the poorest survival rates (Chung et al. 2015). Right heart failure with consecutive circulatory and respiratory collapse constitutes the main cause of death. Right heart dilatation and hypertrophy provoke sinoatrial stretch and reduction in myocardial perfusion, which, in turn, increases the risk of cardiac dysrhythmia. In PAH, approximately 30 % of mortality has recently been reported to be attributable to sudden cardiac death (Bandorski et al. 2015). Hoeper et al. (2002) have investigated the frequency and outcome of cardiopulmonary resuscitation in 132 patients with PAH and demonstrated only a modest survival rate of 6 %, with baseline hemodynamics showing no association with resuscitation outcomes. In that study, initial electrocardiogram at the time of resuscitation revealed ventricular fibrillation present in 8 % of cases.

The autonomic nervous system, which encompasses the sympathetic and parasympathetic neural parts, substantially influences the onset and sustainment of malignant ventricular arrhythmias. Alterations in autonomic nervous system function are evaluable by different approaches, with assessment of heart rate variability (HRV) being of major clinical feasibility. HRV describes the fluctuations of normal heart beat intervals (NN) during ECG-monitoring. In heart failure, atrial fibrillation, stable coronary heart disease and post-myocardial infarction, decreased HRV predicts worse clincial outcome (Valencia et al. 2013), but its diagnostic and prognostic value in pulmonary hypertension still needs to be determined. In the present study we aimed at prospectively evaluating the utility of HRV assessment in pulmonary hypertension by including different pulmonary hypertension classes and comparing the results to controls. Moreover, the respective arrhythmic burden, as assessed by Holter-monitoring, was examined.

2 Methods

2.1 Study Population

The study was approved by the local Ethics Committee and performed in accordance with

the Declaration of Helsinki. Between January 2014 and August 2015, 95 participants, subdivided into four groups, were included in this prospectively conducted trial at the outpatient pneumological department of the University Hospital Bonn (Germany). There were 36 patients with invasively confirmed pre-capillary pulmonary hypertension, of whom 25 patients appertained to group 1 (PAH) and 11 patients to group 4 (CTEPH); the division was made according to the current European Society of Cardiology/European Respiratory Society's guidelines for the diagnosis and treatment of pulmonary hypertension (Galiè et al. 2016; Simonneau et al. 2013). A third subgroup consisted of 28 patients with echocardiographically diagnosed pulmonary hypertension and spirometrically and clinically confirmed advanced, emphysematous chronic obstructive pulmonary disease (COPD). Finally, an age- and gender-matched healthy control group of 31 individuals was included. Controls had no history of cardiac or pulmonary disease.

All participants underwent 24-hour Holter electrocardiogram, recorded by the SpiderView™ Ambulatory Electrocardiographic Recorder (Sorin Group; Milan, Italy). A trained professional applied five electrodes to the subject's chest. Two electrodes were placed parasternal right and left between the second and third rib. One was positioned in the right mid-clavicular line between the seventh and eighth rib, another was positioned on the contralateral left side. The last electrode was placed directly at the xiphoid. An experienced cardiologist analyzed the Holter ECG data using SyneScope™ Software (Sorin Group; Milan, Italy).

Additionally, transthoracic echocardiography was performed the day after Holter monitoring by experienced cardiac sonographers on conventional equipment (iE 33, Philips Medical Systems; Koninklijke N.V., Hamburg, Germany) in line with the recommendations of the American Society of Echocardiography (American College of Cardiology Foundation Appropriate Use Criteria Task Force 2011). In PAH/CTEPH patients, right heart catheterization values were recorded just before the Holter monitoring. A standardized questionnaire-based survey was performed to assess the use of medication.

2.2 Supraventricular and Ventricular Arrhythmias

The SyneScope™ Software analyzes supraventricular und ventricular premature beats and divides them into three groups: single ectopic beats, couplets, and salvos/non-sustained supraventricular and ventricular tachycardias. Additionally, it combines all recognized premature beats to a total number, denominated as premature atrial and ventricular contractions (PAC and PVC, respectively) which were used for statistical analysis.

2.3 Time-Domain Analysis

SyneScope™ Software enables time-domain analysis of HRV. All NN intervals qualify for analysis when in sinus rhythm. All ectopic beats, non-sinus rhythm beats or artifacts are excluded. We analyzed a number of indices: The mean standard deviation of NN intervals (SDNN, in milliseconds) was analyzed over a 24-h period as it is influenced by the circadian rhythm. SDNN values below 100 ms are predictive of increased cardiovascular mortality (Nolan et al. 1998). The mean standard deviation of the average NN intervals (SDANN, in milliseconds) was analyzed for all of the 5-min intervals of 24-h Holter monitoring. The root mean square of differences between successive NN intervals (RMSSD, in milliseconds) is the average absolute value of the variation in NN intervals between single beats. Finally, there is a percentage of NN intervals that differ from the prior interval by at least 50 ms (pNN50%). The indices were correlated to the echocardiographically assessed pulmonary arterial systolic pressure (PASP).