Hidradenitis Suppurativa is Associated with Higher Heart Rate but Not Atrial Fibrillation: A Comparative Cross-sectional Study of 462 Individuals with Hidradenitis Suppurativa in Denmark

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ABSTRACT Hidradenitis suppurativa (HS) is a chronic inflammatory dermatological disease with inflammatory mechanisms overlapping those of psoriasis, and both diseases have been associated with cardiovascular risk factors i.e. smoking and metabolic syndrome. Two studies have recently linked psoriasis with Atrial Fibrillation (AF). AF is the most frequently occurring cardiac arrhythmia in the general population and is typically accompanied by increased heart rate. Both AF and heart rate are linked with inflammation.

The aim of the study was to investigate a potential association between HS and increased heart rate as well as AF.

We performed a comparative cross-sectional study using digital measurements of heart rate and resting 12-lead electrocardiography (ECG) in combination with self-reported information when diagnosing AF.

Our study comprised 32 individuals with HS from the hospital (the hospital HS group), 430 from the general population HS group (the population HS group), and 20,780 controls. Age and sex adjusted analysis demonstrated a significantly higher heart rate in the HS groups vs. controls (15% (range: 8-23%) higher for the hospital HS group and 4% (2-5%) higher for the population HS group). We found no association between HS and AF (P=0.1670).

KEY WORDS: heart rate, atrial fibrillation, arrhythmia, epidemiology, hidradenitis suppurativa (HS), inflammation

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory dermatological disease presenting itself as painful nodules, tunnels, and subsequent scarring of the inverse regions i.e. axillar, inguinal, and anogenital areas(1). Recent studies indicate a prevalence of 2.1% in the general population (2) and a rising incidence (3). HS is associated with smoking as well as a substantial range of psychological and somatic comorbidities such as depression and the cluster of cardiovascular risk factors included in the metabolic syndrome i.e. diabetes, hypertension, dyslipidemia, and obesity (4-6).

Atrial fibrillation (AF) is the most frequently occurring cardiac arrhythmia with a prevalence of 0.4-1.0% of the general population (7), and is associated with increased risk of cardiovascular mortality and morbidity i.e. stroke, heart failure, and myocardial infarction (8,9). In AF, the electrical impulses from the sinoatrial node in the atria are disrupted with a subsequent irregular heart rhythm and often elevated heart rate (7). The pathogenesis is not yet fully understood; however, hypertension, diabetes, obesity, and smoking increase the risk of AF (8,10,11). AF and increased resting heart rate have however both been linked with inflammation. Recently, studies reported the presence of inflammatory cells in the atria, raised inflammatory markers, and oxidative stress in patients with AF(12-20).

The inflammatory pathogenesis in HS is not yet fully understood, but studies suggest involvement of IL-12/Th1, IL-23/Th17 adaptive immune system pathways and TNF-alpha, as in the pathophysiology of psoriasis, but also the involvement of Toll-like receptors, indicating involvement of the innate immune system, i.e. macrophages and dendritic cells (21-25). Interestingly, a recent large study reported increased risk of both AF and stroke in patients with psoriasis from the general population (26). In addition, AF was demonstrated in hypertensive patients with psoriasis (27), and a small study of 32 participants linked psoriasis to raised heart rate and increased frequency of supraventricular extrasystoles(28).

Our objective was to investigate a potential association between HS and increased heart rate as well as AF.

MATERIALS AND METHODS

Ethical statement

This study was accepted by the ethics committee of Region Zealand (project number SJ-191, SJ-113, SJ-114) in Denmark. Written informed consent was obtained from all study participants.

Study design

We performed a comparative cross-sectional study of the association of HS (the exposure) and heart rate as well as atrial fibrillation (the outcomes). We investigated two different HS groups: 1) *A population HS group* identified in a general population sample using a validated questionnaire(2), and 2) *A hospital HS group* identified at a Department of Dermatology by a dermatologist.

The HS groups

The population HS group was identified in the Danish General Suburban Population Study (GESUS), which was a cross-sectional study conducted from January 2010 to October 2013 investigating the adult Danish general suburban population in Naestved Municipality (70 km south of Copenhagen)(29). All citizens aged 30+ and a random selection of those aged 20-30 years were invited. All participants in GESUS answered the GESUS-questionnaire and also underwent a wide spectrum of health examinations.

The HS diagnosis was established if participants self-reported 1) the presence of boils within the previous 6 months as well as 2) a minimum of 2 boils (in 5 possible locations: axillae, groin, genitals, inframammary areas, other – e.g. perianal region, neck, abdomen) in the GESUS-questionnaire. This self-reported HS diagnosis was previously validated showing a sensitivity of 90% and a specificity of 97% (2). The overall participation rate in GESUS was 49.3% (n=10,621 responded from the total n=21,557). Participants were more frequently women and had a higher median age. GESUS had sufficient power to study effects of rare and common exposures. Further details about GESUS can be found in Bergholdt *et al.* (29).

The hospital HS group was recruited from the outpatient clinic at the Department of Dermatology at Roskilde Hospital in Denmark (serving the region of Zealand which includes Naestved). Inclusion criteria were the World Health Organization's International Classification of Diseases (ICD) code, edition 10 (ICD-10) of HS (L73.2) and undergoing either systemic (e.g. rifampicine/clindamycine, tetracycline, cyclosporine, or TNF-alpha inhibitor) or CO2-laser treatment for HS indicating moderate to severe disease. The diagnosis of HS was physician-verified. The participation rate for the invited hospital HS subjects was 34%. The distribution of age and sex did not differ between hospital participants and non-participants (data not shown).

Both HS groups were compared with a control group consisting of participants from GESUS without HS.

Table1. Background factors and characteristics for the hospital hidradenitis suppurativa (HS) group, population HS group, and controls

	Hospital HS-group n=32	**Population HS-group n=430**	**Controls n=20,780**
Age ((years) mean (range))	42 (22-64)	48 (22-78)	56 (20-96)
Sex % (number) Female vs. Male	78% vs. 22%	68% vs. 32%	54% vs. 46%
Smoking Status % (number)			
Present Smoker	55%	41%	18%
Past Smoker	42%	36%	40%
Never Smoked	3%	23%	42%
Ethnicity % (number) Caucasian	97%	97%	99%
CRP (median(mg/l)(range))	5.1 (0.2-119.0)	2.2 (0.1-38.0)	1.3 (0.1-194.0)
HS Severity Distribution			
Mild	12.5%	50%	Not Applicable
Moderate	15.5%	28.5%	Not Applicable
Severe	72%	21.5%	Not Applicable
Sartorius Score (median (range))	29 (5-176)	Not Applicable	Not Applicable
[lower quartile, upper quartile]	[25-50]	Not Applicable	Not Applicable
Number of boils (median (range))	12 (1-171)	3 (2-106)	Not Applicable
[lower quartile, upper quartile]	[11-30]	[3-12.5]	Not Applicable
Body Mass Index Mean (min-max)	31.3(21.5-46.5)	28.85(17.6-47.8)	26.7(14.23-57.5)
Diabetes Mellitus (%)	12.5%	8.3%	6.1%
Self-reported anticoagulent medicine	9.4%	7.2%	10.2%
Left Ventricular Hypertrophia in ECG	0%	0.7%	1.95%
Self-reported artificial heart valves	0%	0.4%	0.4%
Hypertension (self-reported antihypertensive medicine and measured ≥140/90)	56.3%	49.1%	60.8%

Heart rate and atrial fibrillation

Heart rate was measured digitally (Blood Pressure Apparatus type A&D UA-787, A&D Medical, Tokyo, Japan) after 5 minutes of rest in the hospital HS group, the population HS group, as well as the controls. In addition, all population based participants underwent a resting 12-lead electrocardiography (ECG) at 150 Hz (Mac-5500, GE Healthcare, Milwaukee, WI). ECGs were coded according to the automatic ECG analysis program (Marchette 12 SL revision E, GE Healthcare). Both heart rate and ECG measurements of all participants were standardized and performed by trained staff from GESUS.

The diagnosis of atrial fibrillation was established if 1) The participant self-reported non-specified medical treatment for AF ("Are you currently taking medicine for atrial fibrillation? (yes/no)) in the GESUS questionnaire; and/or 2) An automatic ECG code for atrial fibrillation or atrial flutter was given for the participant.

Statistical analyses

For the continuous outcome (heart rate), the mean of each group as well as mean difference was calculated with a corresponding 95% CI and *P*-value. The data was log-transformed before analyses in order to fit the statistical model, and is therefore reported as a Ratio of Means (RM).

The categorical outcome (AF) was reported as Odds Ratio (OR) with a corresponding 95% CI and *P*-value.

Unadjusted RM/OR was calculated. Furthermore, we conducted three regression models (linear regression for the continuous outcome and logistic regression for the categorical outcome) adjusting for background factors and potential confounders: 1) age-sex-adjusted; 2) age-sex-smoking adjusted; 3) age-sex-smoking-BMI (obesity) / DM adjusted; 4) age-sex-smoking-anticoagulant medicine, left ventricular hypertrophy (LVH), artificial heart valves, and hypertension-adjusted.

Additionally, we explored the influence of HS severity by subgroup analysis of all HS participants with severe HS and by regression models investigating a potential association between the continuous outcome and the number of boils, as well as Sartorius score.

The tests were two-sided with the significance level set at 0.05. All analyses were performed using SAS 9.3.

Table 2. Unadjusted data

	Hospital HS group (n=32)	Population HS group (n=430)	Controls (n=20,780)
Heart Rate (Beats per Minute)			
Median (range)	83 (55-113)	74.42 (40-112)	71 (34-160)
lower quartile-upper quartile	75.50-89.50	66-83	64-79
Severe subgroup			
Median (lower quartile-upper quartile)	83 (76-92)	78 (68-86.50)	71 (64-79)
Atrial Fibrillation			
%(No)	Not Applicable No ECG data	1.63% (7)	2.38% (496)
Severe subgroup		1.09% (1)	2.38% (494)

Missing values: 12 (heart rate, controls)
The diagnose atrial fibrillation/flutter (AF) was based on 1) self-reported medical treatment for AF and/or 2) An ECG code for AF (either atrial fibrillation with normal/rapid frequency, atrial flutter either 1:1/1:2/1:3/1:4/1:5/1:>5, atrial flutter with AV-block, atrial fibrillation with premature aberrant complexes, atrial fibrillation with concurrent nodal pacemaker, atrial fibrillation with slow ventricular response, or paroxysmal atrial flutter)

HS Severity

HS severity was explored with 3 different approaches: 1) A non-validated scoring system inspired by but not entirely equivalent to the Hurley score (30) based on self-reported information from the GESUS-questionnaire (Mild HS: minimum 2 boils and no subsequent scarring; moderate HS: minimum 2 boils and subsequent scarring; severe HS: minimum 2 boils in minimum 2 locations and subsequent scarring); 2) Number of self-reported boils; and 3) Sartorius score based on physical examination (30) (the hospital HS group).

RESULTS

Our study comprised a total of 32 individuals in the hospital HS group, 430 in the population HS group, and 20,780 controls. The background factors and characteristics revealed that the HS groups were predominately younger, female, and smokers

Heart rate

Unadjusted data found a higher heart rate for the HS groups when compared with controls (Table 2). Age and sex adjusted analysis demonstrated a significant

Table 3. Unadjusted and adjusted Ratio of Means (RM) and Odds Ratio (OR)

	Hospital HS-group Vs. Controls	Population HS-group Vs. Controls
Heart Rate (Beats per minute)		
I. Unadjusted RM (95% CI)	**1.15 (1.08-1.23)** p<.0001*	**1.03 (1.01-1.05)** p=0.0003*
II. Age-sex adjusted RM (95% CI)	**1.15 (1.08-1.23)** p<.0001*	**1.04 (1.02-1.05)** p<.0001*
III. Age-sex-smoking adjusted RM (95%CI)	**1.13 (1.05-1.20)** p=0.0001*	**1.02 (1.00-1.04)** p=0.0103*
IV. Age-sex-smoking-BMI adjusted RM (95%CI)	**1.08 (1.01-1.57)** p=0.0279*	1.01 (0.99-1.06) p=0.6971
V. Age-sex-smoking-DM adjusted RM (95%CI)	**1.11 (1.04-1.19)** p=0.0007*	1.01 (0.99-1.04) p=0.3219
Atrial Fibrillation/Flutter		
I. Unadjusted OR (95% CI)	Not Applicable No ECG data	0.68 (0.32-1.44) p=0.3162
II. Age-sex adjusted OR (95% CI)		1.72 (0.80-3.71) p=0.1670
III. Age-sex-smoking adjusted OR (95%CI)		1.92 (0.89-4.16) p=0.0984
IV. Age-sex-smoking-anticoagulant medicine, LVH, artificial heart valves, and hypertension adjusted OR (95% CI)		2.14 (0.94-4.90) p=0.0718

RM: Ratio of Means. OR: Odds Ratio. LVH: Left Ventricular Hypertrophia. BMI: Body Mass Index. DM: Diabetes Mellitus
95% CI: 95% confidence interval. *: statistically significant at a 0.05 level

Table 4. Subgroup analysis of severe hidradenitis suppurativa (HS)

	Severe Hospital HS-group (n=18) Vs. Controls	Severe Population HS-group (n=92) Vs. Controls
Heart Rate (Beats per minute)		
I. Unadjusted RM (95% CI)	**1.18 (1.09-1.27)** p<.0001*	**1.08 (1.04-1.13)** p<.0001*
II. Age-sex adjusted RM (95% CI)	**1.18 (1.09-1.27)** p<.0001*	**1.09 (1.05-1.13)** p<.0001*
III. Age-sex-smoking adjusted RM (95%CI)	**1.15 (1.06-1.24)** p=0.0001*	**1.07 (1.03-1.11)** p=0.0003*
Atrial Fibrillation		
I. Unadjusted OR (95% CI)	Not Applicable No ECG data	0.45 (0.06-3.24) p=0.4288
II. Age-sex adjusted OR (95% CI)		1.60 (80.22-11.77) p=0.6489
III. Age-sex-smoking adjusted OR (95%CI)		2.14 (0.29-15.79) p=0.4569
IV. Age-sex-smoking-anticoagulant medicine, LVH, artificial heart valves, and hypertension adjusted OR (95% CI)		2.71 (0.34-21.40) p=0.3450

RMhos of 1.15 (CI 95% 1.08-1.23) and RMpop of 1.04 (1.02-1.05) for the hospital and population HS groups when compared with controls, respectively (Table 3). The hospital-based results remained robust after further adjusting for potential confounders: smoking, obesity and DM (Table 3). The population-based results remained robust after adjusting for smoking; however, they became statistically insignificant when further adjusting for BMI or DM (Table 3).

Atrial fibrillation / flutter (AF)

Both crude data and all adjusted analysis revealed non-significant ORpop for the population HS group vs. controls (Table 3). No patients in the hospital HS group reported medical treatment for AF, and no ECG data was available for the hospital HS group.

HS severity

Subgroup analysis of severe HS groups demonstrated slightly higher RMs of heart rate compared with the above, and the results remained non-significant with regard to AF (Table 4). Regression analysis revealed non-significant association between heart rate and number of boils (P=0.2198), heart rate and Sartorius score (P=0.4392) as well as AF and number of boils (0.6672).

DISCUSSION

This current novel study demonstrated a higher heart rate in HS groups compared with controls, but, in contrast to our hypothesis, no association between HS and AF was found.

Heart rate is highly influenced by the central nervous system as it is mainly controlled by the autonomic nervous system, i.e. sympathetic/parasympathetic activity. Heart rate furthermore varies according to the body's physical needs, medical conditions e.g. hyperthyroidism, psychological state e.g. anxiety/stress, and drugs (31,32).

Accumulating evidence indicated a connection between inflammation and heart rate. Higher heart rate along with reduced heart rate variability was associated with subclinical inflammation in otherwise healthy people when using C-reactive protein as an inflammatory marker (33). TNF-alpha, which has been shown to be elevated in HS, has been found to exhibit toxic effects on cardiomyocytes (34,35), and other inflammatory markers such as thromboxane A2 and prostaglandin F2alpha have been found to mediate inflammatory tachycardia (heart rate above 100 beat/minute) (36). Furthermore, a study proposed that inflammatory reactions and oxidative stress may be involved in tachycardia-induced heart failure (37). Endotoxin injection mimicking acute inflammation was observed to induce tachycardia and raised systolic blood pressure in mice and humans (38). Although heart rates were not high enough to be classified as tachycardia, HS patients exhibited a higher median heart rate compared with healthy controls (crude median 83 beats/minute for hospital HS group, 74.42 beats/minute for population HS group vs. 71 beats/minute for controls). Set side by side with psoriasis, which is as mentioned also an inflammatory skin disease involving Th1 cells, a significantly higher mean heart rate of 88 beats/minute for patients with psoriasis vs. 73 beats/minute for controls was noted in a previous study (28). We could not demonstrate a convincing dose-response relationship when exploring HS severity, suggesting no causal

relationship. However, the measurement of HS severity may not have been optimal, and the small hospital sample may result in lack of power.

The clinical significance of the findings in this study is unknown. Looking at general health, high resting heart rate has been found to be associated with higher age, low physical fitness level, hyperthyroidism, obesity, hypertension, diabetes, metabolic syndrome, psychological stress (involving the autonomic nerve system), higher mortality, and reduced longevity, suggesting several possible co-factors in patients with HS (31,39-43). On an experimental basis, reduction of heart rate in mice by 14% has been found to increase longevity by 6.2% (44). Notably, hyperthyroidism has been linked with HS (43,45). When adjusting for the most prominent co-factors i.e. obesity (BMI) and diabetes, the association between higher heart rate and hidradenitis was reduced but remained significant for the hospital-based HS group but not for the population-based HS group. Thus, obesity and diabetes may act as partial confounders.

We found no association between AF and HS. Our hypothesis predicted an association based on immunological similarities with psoriasis which has recently been associated with AF in a large population-based cohort as well as in a cohort of hypertensive patients with psoriasis (26,27). However, one small study using the Holter method analyzed by Cardioscan software found no complex arrhythmia but only single supraventricular extrasystoles significantly more frequently in patients with psoriasis than controls(28).

Rejection of the a priori hypothesis often poses a challenge. Non-significant results contain an equal amount of scientific information; however, potential interpretations appear less forthright as absence of evidence is not the same as evidence of absence (46). Potential explanations may be postulated regarding the link between AF and psoriasis, but not HS. The inflammatory profiles of psoriasis and HS are not similar but do overlap. The relation between inflammation and AF may be exhibited by pro-arrhythmic effects of cytokines like TNF-alpha (47,48). Tissue levels of TNF-alpha are however higher in HS than in psoriasis, and other mechanisms may therefore be of interest (25).

Hypertension predisposes AF. Two of the studies on the link between the individual MetS-components and HS suggest that the weakest association is that of hypertension. A study we previously conducted on the same group of GESUS-patients found a non-significant association to hypertension (42). Sabat *et al.* found that the average systolic and diastolic blood pressure was significantly higher in patients with HS vs. controls, but the frequency of actual hypertension was not higher (49). Thus, the lack of association between HS and AF when compared with the existing association between psoriasis and AF may be attributed to the fact that the association between psoriasis and hypertension is stronger than that of HS and hypertension. However, adjustments for higher average systolic and diastolic blood preasure did not change the results. Furthermore, our control group had 2.38% patients with a diagnosis of AF (Table 2), which is high compared with the general AF prevalence of 0.4-1% reported in previous studies (7). In fact, the population HS group had a higher percentage of patients with AF compared with the general AF prevalence (1.63% vs 0.4-1%) (Table 2).

Finally, one explanation for these results could simply be the methodological differences between the psoriasis studies and the current study.

One of the considerable shortcomings of the current study is the method of diagnosing AF, which was based on ECG automatic coding at a single point in time. On the other hand, the AF diagnosis also includes self-reported medical treatment of AF. The two previously conducted studies on the possible association of psoriasis and AF may have benefitted from more optimized methods of diagnosing AF, namely according to Minnesota coding or ICD-10 codes from a previously validated National Patients Registry, yielding 99% of confirmed AF diagnoses (26,27). Further notable limitations are the potential sources of selection bias possibly hampering the generalizability: the population is suburban, Caucasian, and the low participation rate of the hospital HS group may represent only the healthiest HS patients. Furthermore, we did not have ECG data on the hospital group.

The primary advantages of our study are the large and broad inclusion, i.e. including HS patients from both a hospital environment as well as the general population and mild to severe HS, yielding high power as well as reduced selection bias and thus aiding generalization. Possible misclassification bias, e.g. un / misdiagnosed HS patients, was minimized by using previously validated self-reported questions referring to symptoms (i.e. boils) rather than the actual diagnosis (i.e. "do you suffer from HS?") (2). The diagnosis for hospital HS was physician-verified. Finally, potential confounders were explored.

As predicted by our hypothesis, HS was associated with a higher heart rate compared with controls. However, HS was not associated with AF.

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