Blood-based 8-hydroxy-2′-deoxyguanosine level: A potential diagnostic biomarker for atrial fibrillation

Jin Li, MD,* Deli Zhang, PhD,*† Kennedy S. Ramos, MD,*‡ Luciënne Baks, MSc,* Marit Wiersma, PhD,* Eva A.H. Lanters, MD,‡ Ad J.J.C. Bogers, MD, PhD,§ Natasja M.S. de Groot, MD, PhD,‡ Bianca J.J.M. Brundel, PhD*

*From the *Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centers, Department of Physiology, Amsterdam, The Netherlands, †Department of Human and Animal Physiology, Wageningen University and Research, Wageningen, The Netherlands, ‡Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands, and §Department of Cardiothoracic Surgery, Erasmus Medical Center, Rotterdam, The Netherlands.*

BACKGROUND Recent research findings have revealed a key role of oxidative DNA damage in the pathogenesis of atrial fibrillation (AF). Therefore, the circulating oxidative DNA damage marker 8-hydroxy-2′-deoxyguanosine (8-OHdG) may represent a biomarker for staging AF and identifying patients at risk for AF recurrence and postoperative atrial fibrillation (POAF) after treatment.

OBJECTIVE The purpose of this study was to investigate whether serum levels of 8-OHdG correlate with the stage of AF, recurrence after AF treatment, and onset of POAF after cardiac surgery.

METHODS In this prospective observational study, 8-OHdG levels were detected by enzyme-linked immunosorbent assay in human serum samples. Blood samples were collected from control patients without AF history; patients with paroxysmal AF and persistent AF undergoing electrical cardioversion or pulmonary vein isolation (PVI); and patients with sinus rhythm (SR) undergoing cardiac surgery. AF recurrence was determined during 12-month follow-up. Univariate and multivariate analyses were used to identify changes in 8-OHdG levels between the groups.

RESULTS Compared to the control group, 8-OHdG levels in the patient groups gradually and significantly increased during arrhythmia progression. 8-OHdG levels in AF patients showing AF recurrence after PVI treatment were significantly increased compared to patients without AF recurrence. Moreover, in SR patients undergoing cardiac surgery, 8-OHdG levels were significantly elevated in those showing POAF compared to patients without POAF.

CONCLUSION 8-OHdG level may represent a potential diagnostic biomarker for AF staging as well as for predicting AF recurrence and POAF after treatment.

KEYWORDS 8-hydroxy-2′-deoxyguanosine; Atrial fibrillation; Biomarker; DNA damage; Postoperative atrial fibrillation

(Heart Rhythm 2020;■:1–7)

Introduction

Atrial fibrillation (AF) is the most common progressive tachyarrhythmia and is associated with serious complications such as heart failure and stroke.[1] Due to the aging population, the prevalence of AF is steadily rising, especially in the population between 75 and 85 years of age.[2] AF increases morbidity and mortality rates, with a 5-fold increased risk of stroke and a 3-fold increased risk of congestive heart failure.[2] Therefore, AF contributes to medical and economic problems worldwide.[3,4] In addition, 30%–50% of patients who undergo cardiac surgery develop postoperative atrial fibrillation (POAF).[5,6] POAF frequently occurs within 5 days after surgery, with a peak incidence on postoperative day 2.[5,7] Patients who develop POAF may require a longer period of hospitalization because POAF is associated with a higher risk of other postoperative complications, such as stroke and perioperative myocardial infarction.[5,8]

Early recognition and staging of AF are essential to initiate treatment to prevent disease progression. AF progression is accompanied by a congruent increase in therapy failure and in the end stage cannot, even with extensive therapy, be treated.[9–11] At present, AF can only be diagnosed with a surface electrocardiogram when the patient has already

This project was funded by the LSH-Impulse Grant 40-43100-98-008; the Dutch Heart Foundation (2013T144, 2013T096, 2017T029 and 2020B003); CVON-STW2016-14728 AFFIP; and Medical Delta, the Netherlands. The authors have no conflicts of interest to disclose. **Address reprint requests and correspondence:** Dr Bianca Brundel, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centers, Department of Physiology, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. E-mail address: b.brundel@amsterdamumc.nl.

 https://doi.org/10.1016/j.hrthm.2020.09.017

experienced AF. However, no effective diagnostic tool is available for staging AF. Therefore, diagnostic biomarkers that can stage and possibly predict AF are clinical highly relevant.[10]

Emerging evidence indicates that AF is intimately linked with DNA damage in experimental AF models and in patients with persistent AF. A recent study using experimental AF models revealed that electrical and contractile impairment of atrial cardiomyocytes is precipitated by nicotinamide adenine dinucleotide (NAD^+) depletion via excessive poly(ADP)-ribose polymerase 1 (PARP1) activation in response to oxidative DNA damage.[12] PARP1-mediated synthesis of ADP ribose chains, in turn, depletes NAD^+ levels, thereby inducing further oxidative DNA damage and electrical and contractile dysfunction, which drives AF progression.[12,13] Consistent with these findings, cardiomyocytes of patients with persistent AF show significant oxidative DNA damage in atrial tissue, characterized by an elevated level of phosphorylated histone 2A family member X (H2AX), forming γ-H2AX, which is an early response to the induction of DNA double-strand breaks.[12,14,15] Based on these findings, we hypothesize that oxidative DNA damage represents a potential biomarker for staging AF and predicting AF recurrence. Interestingly, 8-hydroxy-2′-deoxyguanosine (8-OHdG) is an important byproduct of oxidative DNA damage, which is formed during the repair of damaged DNA by exonucleases.[16] As 8-OHdG is circulating in the blood after oxidative damage in DNA, it may represent a biomarker for AF.[17] In this study, we correlated serum 8-OHdG levels with AF stage and recurrence after AF therapy, and tested whether 8-OHdG predicts POAF in patients with sinus rhythm (SR) undergoing cardiac surgery.

Methods

Patient characteristics

In this prospective observational study, 257 serum samples were collected from patients 1 day before cardiac surgery, pulmonary vein isolation (PVI), or electrical cardioversion (ECV) and from control patients at the cardiology department at the Erasmus Medical Center (Rotterdam, The Netherlands). To study 8-OHdG levels in various AF stages, the following groups were included: control group (control; N = 50), paroxysmal AF group (PAF; N = 74), and persistent AF group (PeAF; N = 89). To study 8-OHdG levels in POAF, a group of patients in SR undergoing cardiac surgery (N = 44) were included. Detailed clinical characteristics of the control and AF patients are given in the Supplemental Methods. All AF patients were treated with anticoagulants and signed consent forms before inclusion in the study. This substudy is part of the HALT & REVERSE (Hsf1 Activators Lower Cardiomyocyte damage: Towards a novel approach to REVERSE atrial fibrillation) trial (Rotterdam Medical Ethical Committee MEC-2014-393) and is approved by the institutional medical ethical committee. The study was performed according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Committee Involving Human Subjects Act.

DNA damage marker 8-OHdG measurement

Blood samples were collected for measurement of the DNA damage marker 8-OHdG. Details are available in the Supplemental Methods.

Statistical analysis

Quantitative data are given as mean ± SD. Statistical analyses were performed using SPSS Statistics Version 26.0 for Windows (SPSS, Chicago, IL) and GraphPad Prism Version 8.0 (GraphPad Software, San Diego, CA). If data were not normally distributed, then log10 transformation was performed before statistical analysis. One-way analysis of variance (ANOVA) and *post hoc* Tukey tests were used to assess 8-OHdG levels in each group. Two-way ANOVA and *post hoc* Tukey tests were used to assess sex differences. Differences in clinical characteristics between control, PAF, and PeAF were tested with 1-way ANOVA, Kruskal-Wallis test, and χ^2 test. Differences in clinical characteristics between patients with and those without AF recurrence were tested with independent-samples Student *t* test, Mann-Whitney test, and χ^2 test. Levels of 8-OHdG in patients with or those without AF recurrence in the AF group and levels of 8-OHdG in patients with or those without POAF in the SR group were compared using the nonparametric Mann-Whitney test. Linear regression was used for age, body mass index (BMI), hypertension, diabetes, and antiarrhythmic drug class I (AAD-I) correction. A receiver operating characteristic (ROC) curve was used to analyze the diagnostic power of 8-OHdG. All *P* values were 2-sided, and $P < .05$ was considered significant.

Results

Clinical characteristics

To study the correlation between 8-OHdG and AF stage, 213 patients were included in the study: a control group of patients (N = 50 [23%]) without AF and a study group of 163 AF patients with either PAF (N = 74 [35%]) or PeAF (N = 89 [42%]). Table 1 lists the characteristics of the study population. Patients with AF were older ($P < .05$), presented with higher BMI ($P < .05$), more often had hypertension and diabetes ($P < .05$), had a larger left atrial volume ($P < .05$), and presented with more impaired left ventricular function ($P < .05$) compared to control patients without AF.

Serum levels of 8-OHdG stage AF

To test whether oxidative DNA damage is associated with AF stage, we measured the level of 8-OHdG in the serum samples of the patient population (Table 1). Compared to the control patients, serum 8-OHdG levels were gradually and significantly increased in PAF and PeAF patients (control vs PAF: 6.76 ± 2.77 ng/mL vs 8.33 ± 4.11 ng/mL; $P = .018$; PAF vs PeAF: 8.33 ± 4.11 ng/mL vs 10.52 ± 4.22 ng/mL; $P = .001$) even after correction for age, BMI, hypertension, and

Table 1 Characteristics of patients included for 8-OHdG analysis in serum samples (N = 213)

	Control	PAF	PeAF	*P* value	
	(n = 50)	(n = 74)	(n = 89)	Control vs PAF	Control vs PeAF
Male sex	25 (50.0)	51 (68.9)	61 (68.5)	.034	.031
Age (yr)	49.6 ± 14.8	60.5 ± 10.2	60.6 ± 10.2	<.001	<.001
BMI (kg/m^2)	24.6 ± 3.7	28.6 ± 5.0	28.5 ± 4.9	<.001	<.001
Hypertension	12 (24.0)	36 (48.6)	43 (48.3)	.006	.005
Diabetes	1 (2.0)	8 (10.8)	8 (9.0)	.043	.157
PVI		63	25		
ECV		11	64		
Underlying heart disease					
WPW syndrome	5 (10.0)	0 (0.0)	0 (0.0)		
PVCs	21 (42.0)	0 (0.0)	0 (0.0)		
LAD >45 mm (%)	0 (0.0)	25 (33.8)	38 (42.7)	<.001	<.001
LVF					
Normal	32 (85)	64 (86.5)	52 (58.4)	.519	.003
Mild impairment	5 (12.5)	6 (8.1)	26 (29.2)	.716	.009
Moderate impairment	3 (7.5)	3 (4.1)	8 (9.0)	.684	.746
Severe impairment	0 (0.0)	1 (1.4)	4 (4.5)	1	.297
Medication					
ACE inhibitor	15 (30.0)	34 (46.0)	43 (48.3)	.075	.036
Statin	10 (20.0)	30 (40.5)	35 (39.3)	.016	.019
Type I AAD	3 (6.0)	27 (36.5)	14 (15.7)	<.001	.111
Type II AAD	17 (34.0)	31 (41.9)	43 (48.3)	.376	.102
Type III AAD	4 (8.0)	37 (50.0)	48 (53.9)	<.001	<.001
Type IV AAD	1 (2.0)	4 (5.4)	6 (6.7)	.647	.421
Digoxin	0 (0.0)	5 (6.8)	15 (16.9)	.081	.001

Values are given as n (%) or mean ± SD unless otherwise indicated.

8-OHdG = 8-hydroxy-2′-deoxyguanosine; AAD = antiarrhythmic drug; ACE = angiotensin-converting enzyme; BMI = body mass index; ECV = electrical cardioversion; LAD = left atrial dilation; LVF = left ventricular function; PAF = paroxysmal atrial fibrillation; PeAF = persistent atrial fibrillation; PVC = premature ventricular contraction; PVI = pulmonary vein isolation; WPW = Wolff-Parkinson-White.

diabetes with linear regression (Figure 1A). No differences in 8-OHdG levels were observed between males and females (Figure 1B). The findings indicate that the oxidative DNA damage marker 8-OHdG gradually increases in more advanced stages of AF and that this effect is sex independent.

Diagnostic value of 8-OHdG as a blood-based biomarker for AF

To determine whether the serum level of 8-OHdG has power to discriminate AF patients from controls, an ROC curve was constructed. Figure 2 shows an area under the curve (AUC) of 71%, which corresponds to sensitivity of 80% and specificity of 44%. These findings indicate that 8-OHdG levels have value in discriminating between AF patients and controls and therefore may represent an independent and valuable diagnostic biomarker for AF.

Relation between 8-OHdG levels and AF recurrence

To investigate a relation between serum 8-OHdG levels and AF recurrence after PVI or ECV treatment, we compared 8-OHdG levels in the AF population between patients with and those without AF recurrence after treatment. Clinical parameters are listed in Table 2. In the PVI group, patients with AF recurrence after PVI treatment presented more often with hypertension (P <.05) than did patients without AF recurrence. However, patients without AF recurrence after PVI treatment more often received treatment with AAD-I (P <.05) compared to patients with AF recurrence. In the ECV group, patients with AF recurrence after ECV treatment presented more often with hypertension (P <.05) than did patients without AF recurrence (Table 2). In addition, 54% of PVI patients and 59% of ECV patients experienced AF recurrence within 12 months. Levels of 8-OHdG in patients with AF recurrence after PVI treatment are significantly higher (no recurrence vs recurrence: 7.35 ± 3.23 ng/mL vs 9.55 ± 4.14 ng/mL; P = .018) compared to patients without AF recurrence, even after correction for hypertension and AAD-I treatment with linear regression (Figure 3A). No differences in serum levels of 8-OHdG was found in AF patients with AF recurrence after ECV treatment compared to those without AF recurrence (no recurrence vs recurrence: 9.76 ± 3.09 ng/mL vs 10.99 ± 4.72 ng/mL; P = .214) (Figure 3B).

Relation between 8-OHdG levels and POAF

Oxidative stress is an important contributor to POAF.[18,19] Therefore, we evaluated 8-OHdG levels in SR patients undergoing cardiac surgery and correlated the levels with development of POAF. Characteristics of the study population are listed in Table 3. Clinical parameters, including sex, age, and left atrial dilation were comparable between SR patients with and those without POAF after cardiac surgery. Compared to SR patients without POAF, 8-OHdG levels in patients with POAF were significantly increased (9.76 ± 5.42 ng/mL vs 10.82 ± 5.58 ng/mL; P <.001) (Figure 4). This finding indicates that preoperative 8-OHdG levels are

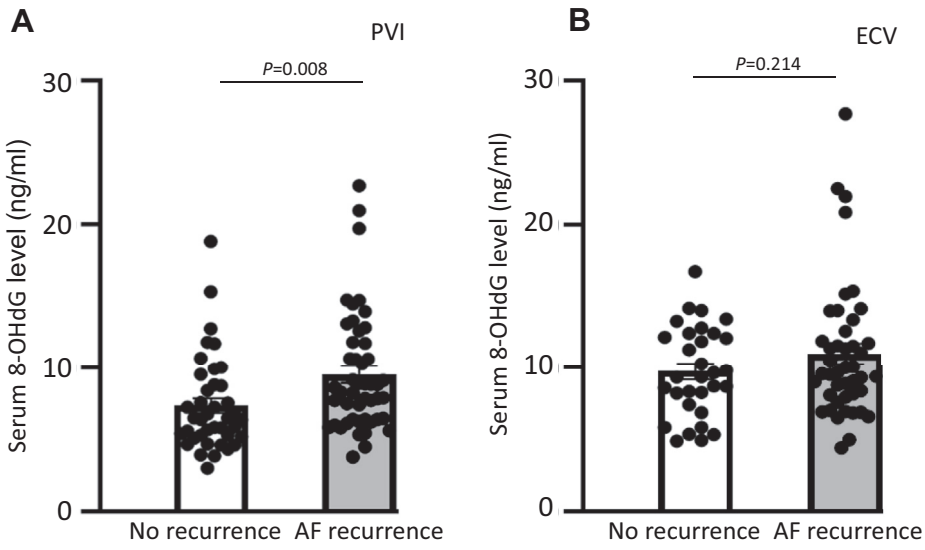

Figure 1 Serum levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG) gradually and significantly increase in patients with atrial fibrillation (AF) compared to controls. **A:** Levels of 8-OHdG in human serum samples of AF patients and controls. Compared to the control group, 8-OHdG levels in patients with paroxysmal atrial fibrillation (PAF) and persistent atrial fibrillation (PeAF) were significantly increased. Compared to PAF, 8-OHdG levels in patients with PeAF were significantly increased. Control: N = 50; PAF: N = 74; PeAF: N = 89. **B:** Levels of 8-OHdG in serum samples from male and female patients with AF or controls in sinus rhythm. There was no significant difference between male and female patients for all groups. Control, male: N = 23; control, female: N = 27; PAF, male: N = 52; PAF female: N = 22; PeAF, male: N = 61; PeAF female: N = 28.

correlated with POAF and therefore may represent a potential predictor of POAF in SR patients undergoing cardiac surgery.

Discussion

In this study, we observed that levels of the oxidative DNA damage marker 8-OHdG before PVI or ECV treatment were significantly increased during more persistent stages of AF. Also, 8-OHdG levels in patients with an AF recurrence after PVI treatment were significantly increased compared to patients without AF recurrence within 12 months of follow-up. Importantly, the level of 8-OHdG is independent of patient characteristics in all groups studied. Moreover, SR patients undergoing cardiac surgery had elevated levels of 8-OHdG in case of POAF onset compared to patients without POAF. Thus, our findings indicate that 8-OHdG levels may have diagnostic value in staging AF and predicting AF recurrence after PVI and POAF onset following cardiac surgery.

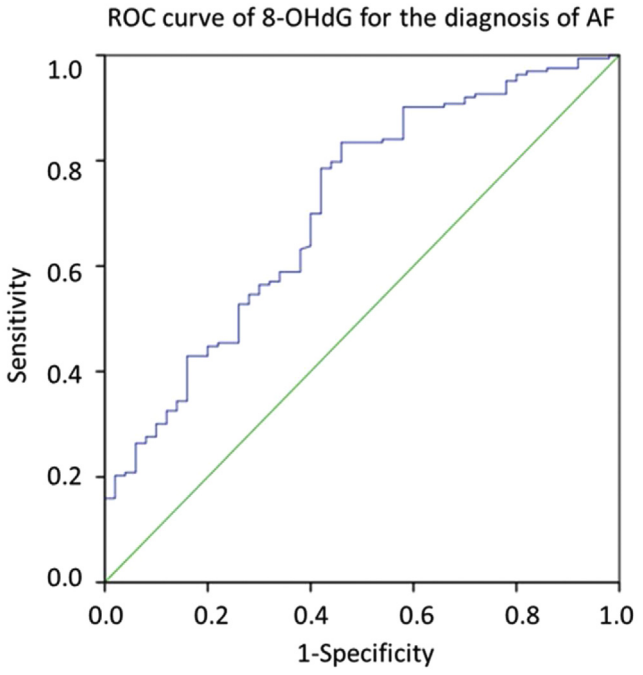

Figure 2 Diagnostic value of serum 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels in atrial fibrillation (AF). Receiver operating characteristic (ROC) curve with an area under the curve of 71%, which corresponds to sensitivity of 80% and specificity of 44%. N = 213 samples.

Serum 8-OHdG level as potential biomarker for AF

Although AF is diagnosed with an electrocardiogram, the stage of AF cannot be determined. Previous biomarker studies reported associations between cardiac troponin T, troponin I, natriuretic peptide, transforming growth factor-beta, and tissue inhibitor of metalloproteinase-1 levels with AF.[20–24] However, whether these biomarkers could stage AF and predict AF recurrence after PVI treatment is unknown.[25] Our previous study identified a key role of oxidative DNA damage in driving experimental and clinical AF.[12] Based on these mechanistic findings, we investigated oxidative DNA damage levels in serum samples of AF patients. In line with the mechanistic DNA damage study, the current study reports that the marker for oxidative DNA damage, 8-OHdG, can discriminate 3 relevant AF patient populations from controls. These 3 discriminated AF populations include patients in the various AF stages from controls without AF; patients with an AF recurrence after PVI from patients without recurrence within 12 months of follow-up; and patients who develop POAF from patients without POAF.

Table 2 Characteristics of patients undergoing PVI or ECV treatment used for 8-OHdG analysis in serum (N = 163)

	PVI		*P* value	ECV		
AF recurrence	No	Yes		No	Yes	*P* value
No.	40	48		31	44	
PAF	36	27	.001	3	10	.216
PeAF	4	21	.001	28	34	.216
Male sex	30 (75.0)	31 (64.6)	.291	21 (67.7)	32 (72.7)	.176
Age (yr)	58.7 ± 8.9	62.0 ± 9.6	.100	58.4 ± 9.2	62.5 ± 11.9	.067
BMI (kg/m^2)	27.7 ± 4.0	27.8 ± 4.3	.869	30.5 ± 7.3	28.5 ± 3.7	.112
Hypertension	12 (30.0)	28 (58.3)	.008	10 (32.3)	24 (54.5)	.056
Diabetes	2 (5.0)	8 (16.7)	.104	5 (16.1)	3 (6.8)	.263
LAD >45 mm (%)	11 (27.5)	20 (41.7)	.066	11 (35.5)	20 (45.5)	.388
LVF						
Normal	36 (90.0)	37 (77.1)	.156	16 (51.6)	25 (56.8)	.656
Mild impairment	3 (7.5)	9 (18.8)	.211	9 (29.0)	12 (27.3)	.867
Moderate impairment	1 (2.5)	2 (4.2)	1	3 (9.7)	5 (11.4)	1
Severe impairment	0 (0.0)	0 (0.0)		3 (9.7)	1 (2.3)	.300
Medication						
ACE inhibitor	13 (32.5)	22 (45.8)	.203	15 (48.4)	27 (61.4)	.165
Statin	13 (32.5)	22 (45.8)	.203	10 (32.3)	19 (43.2)	.339
Type I AAD	19 (47.5)	13 (27.1)	.047	1 (3.2)	8 (18.2)	.072
Type II AAD	15 (37.5)	20 (41.7)	.691	15 (48.4)	22 (50.0)	.891
Type III AAD	21 (52.5)	29 (60.4)	.455	15 (48.4)	19 (43.2)	.656
Type IV AAD	1 (2.5)	4 (8.3)	.371	2 (6.5)	3 (6.8)	1
Digoxin	4 (10.0)	3 (6.3)	.697	3 (9.7)	9 (20.5)	.338
AF recurrence (12-mo follow-up)	54.5%			58.6%		

Values are given as n, n (%), or mean ± SD unless otherwise indicated.
AF = atrial fibrillation; other abbreviations as in Table 1.

To date, only 1 previous study has reported on the role of 8-OHdG as a biomarker for AF. In that study, 8-OHdG levels were found to be increased in urine samples of AF patients compared to controls in SR, and the levels were reduced after ECV or ablative therapy.[26] No data on prediction of AF recurrence and POAF have been reported to date. Interestingly, in the current study, ROC curve values indicate that the level of 8-OHdG in serum has

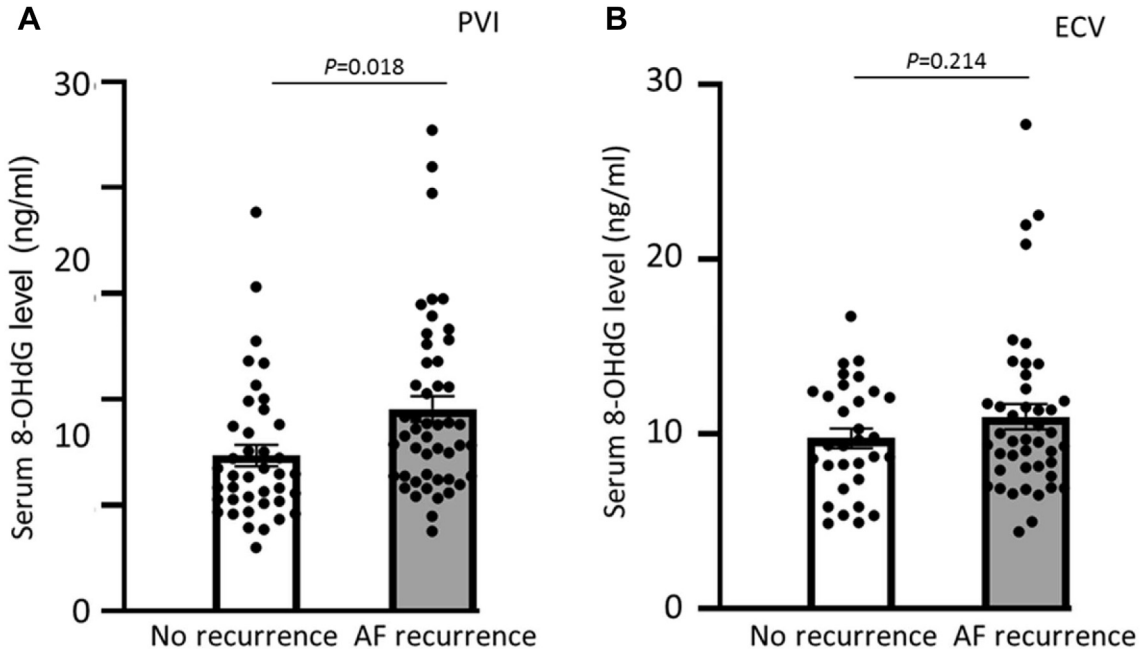

Figure 3 Serum levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG) in atrial fibrillation (AF) patients with AF recurrence after pulmonary vein isolation (PVI) treatment were increased compared to patients without AF recurrence. **A:** 8-OHdG levels in serum samples of AF patients with (N = 48) and those without (N = 40) AF recurrence within 12 months after PVI treatment. Compared to the group of patients without AF recurrence, the level of 8-OHdG in patients with AF recurrence was significantly increased. **B:** 8-OHdG levels in serum samples of AF patients with (N = 44) and those without (N = 31) AF recurrence after electrical cardioversion (ECV) treatment. No difference was observed in 8-OHdG levels in serum samples of patients with and those without AF recurrence after ECV.

Table 3 Patient characteristics used for 8-OHdG analysis with/without POAF in serum (N = 44)

	SR without POAF (n = 21)	SR with POAF (n = 23)	*P* value
Male sex	19 (90.4)	18 (78.3)	.416
Age (yr)	68.0 ± 9.0	69.8 ± 8.7	.739
BMI (kg/m^2)	28.4 ± 4.1	28.2 ± 4.1	.993
Hypertension	15 (71.4)	13 (56.5)	.305
Diabetes	8 (38.1)	4 (17.4)	.179
Underlying heart disease			
CAD	16 (76.1)	15 (65.2)	.426
AVD	0 (0.0)	2 (8.7)	.489
AVD + CABG	3 (14.3)	3 (13.0)	1
MVD	1 (4.8)	2 (8.7)	1
MVD + CABG	1 (4.8)	1 (4.4)	1
LAD >45 mm (%)	0 (0.0)	3 (13.0)	.234
LVF			
Normal	15 (71.4)	21 (91.3)	.126
Mild impairment	6 (28.6)	2 (8.7)	.126
Moderate impairment	0 (0.0)	0 (0.0)	
Severe impairment	0 (0.0)	0 (0.0)	
Medication			
ACE inhibitor	14 (66.7)	14 (60.9)	.690
Statin	17 (81.0)	17 (73.9)	.724
Type I AAD	0 (0.0)	1 (4.3)	.334
Type II AAD	15 (71.4)	16 (69.6)	.892
Type III AAD	0 (0.0)	0 (0.0)	
Type IV AAD	2 (9.5)	2 (8.7)	1
Digoxin	0 (0.0)	0 (0.0)	

Values are n (%) or mean ± SD unless otherwise indicated.

AVD = aortic valve disease; CABG = coronary artery bypass graft; CAD = coronary artery disease; MVD = mitral valve disease; POAF = postoperative atrial fibrillation; SR = sinus rhythm; other abbreviation as in Table 1.

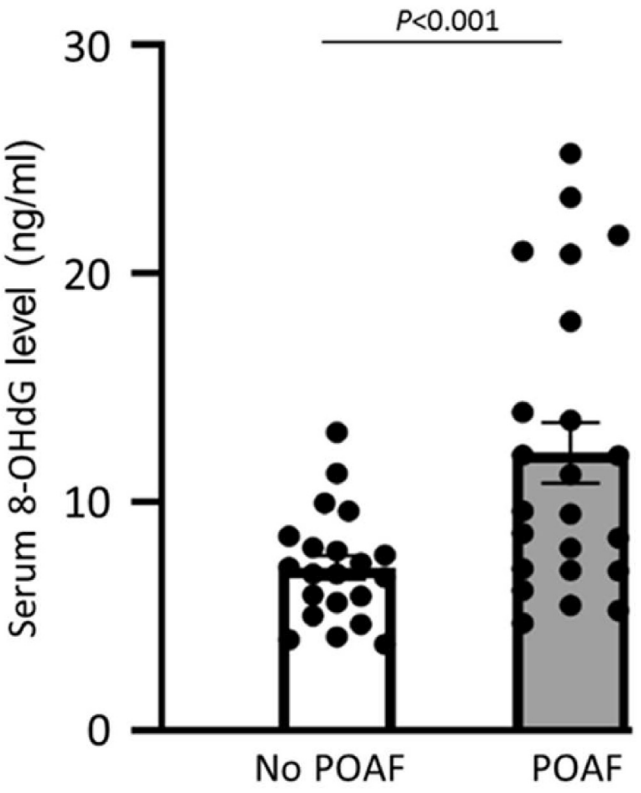

Figure 4 8-Hydroxy-2′-deoxyguanosine (8-OHdG) levels in serum samples of sinus rhythm (SR) patients with postoperative atrial fibrillation (POAF) after cardiac surgery were significantly elevated compared to levels in SR patients without POAF. The level of 8-OHdG in the serum samples of SR patients with (N = 23) and those without (N = 21) POAF after cardiac surgery are shown. Compared to the group of patients without POAF, the level of 8-OHdG in SR patients with POAF was significantly elevated.

sufficient power to discriminate AF patients from controls. Therefore, serum 8-OHdG levels may have diagnostic value as a biomarker for identifying AF stage and recurrence in patients.

Serum 8-OHdG levels predict POAF

The etiology of POAF is considered to be multifactorial and involves a complex interaction of "triggering" stimuli and "sustaining" processes acting on a myocardial substrate that may be predisposed to developing AF.[27] Recently, inflammation and oxidative damage have been identified as key contributors to POAF.[18,27] Surgical trauma, ischemia during both cardiopulmonary bypass and cardioplegic arrest, and reperfusion contribute to induction of oxidative damage and the production of proinflammatory molecules including interleukin-6, tumor necrosis factor-α, and C-reactive protein.[27–29] Moreover, cardiopulmonary bypass and cardioplegic arrest–related oxidative stress may trigger cellular changes in atrial tissue and lead to disruption of electrical activity.[18,30] The main atrial remodeling associated with the pathogenesis of POAF is production of reactive oxygen species, primarily via enhanced NADPH oxidase activity due to mitochondrial dysfunction in atrial cardiomyocytes.[31,32] Interestingly, in the current study, preoperative 8-OHdG levels in SR patients who developed POAF after cardiac surgery were significantly increased compared to patients without POAF. This suggests that oxidative DNA damage may be associated with onset of POAF, so these levels may predict the chance of development of POAF in SR patients after cardiac surgery. Future research is warranted to confirm this finding and elucidate the exact mechanism of how the oxidative DNA damage pathway may contribute to POAF onset.

Study limitations and perspectives

This study reports that serum 8-OHdG levels in AF patients are closely linked to AF staging and recurrences after ablative therapy. Furthermore, 8-OHdG may have value in predicting the chance of development of POAF in SR patients after cardiac surgery. However, 2 key limitations need to be addressed. First, the sample sizes were limited. Based on the present data, larger-scale prospective trials are warranted to further establish the relation between 8-OHdG levels in various AF stages and their power to discriminate patients with AF recurrence from nonrecurrence after various treatment strategies. Second, the pathophysiology of AF and POAF are complex and multifactorial; therefore, in order to further improve the diagnostic power of biomarkers, including improved sensitivity and specificity of a marker, it may be helpful to combine 8-OHdG levels with other

AF-related markers. Additional markers may include phosphorylated H2AX, NAD^+, and NADH levels.

Conclusion

The level of 8-OHdG is closely linked with the stage of AF, as the level gradually increases during more advanced stages of AF. 8-OHdG levels may predict AF recurrence after ablative therapy and POAF onset after surgical treatment of cardiovascular diseases. The level of 8-OHdG may represent a potential diagnostic biomarker for staging AF and predicting AF recurrence after ablative therapy and POAF after cardiac surgery.

Acknowledgments

The authors acknowledge all patients who participated in this study, and thank the staff and personnel of the Department of Cardiology of the Erasmus Medical Center Rotterdam for their help in collecting serum samples from the patients.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2020.09.017.

References

1. Pellman J, Sheikh F. Atrial fibrillation: mechanisms, therapeutics, and future directions. Compr Physiol 2015;5:649–665.
2. Camm AJ, Lip GY, De Caterina R, et al; ESC Committee for Practice Guidelines-CPG; Document Reviewers. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation—developed with the special contribution of the European Heart Rhythm Association. Europace 2012;14:1385–1413.
3. Lee TI, Bai KJ, Chen YC, et al. Histone deacetylase inhibition of cardiac autophagy in rats on a highfat diet with lowdose streptozotocin-induced type 2 diabetes mellitus. Mol Med Rep 2018;17:594–601.
4. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death. Circulation 1998;98:946–952.
5. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008;51:793–801.
6. Auer J, Weber T, Berent R, Ng CK, Lamm G, Eber B. Risk factors of postoperative atrial fibrillation after cardiac surgery. J Card Surg 2005;20:425–431.
7. Yaksh A, Kik C, Knops P, van Ettinger MJ, Bogers AJ, de Groot NM. Early, de novo atrial fibrillation after coronary artery bypass grafting: facts and features. Am Heart J 2017;184:62–70.
8. Attaran S, Shaw M, Bond L, Pullan MD, Fabri BM. Atrial fibrillation postcardiac surgery: a common but a morbid complication. Interact Cardiovasc Thorac Surg 2011;12:772–777.
9. Heijman J, Guichard JB, Dobrev D, Nattel S. Translational challenges in atrial fibrillation. Circ Res 2018;122:752–773.
10. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–2962.
11. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol 2014;6:213–220.
12. Zhang D, Hu X, Li J, et al. DNA damage-induced PARP1 activation confers cardiomyocyte dysfunction through NAD(+) depletion in experimental atrial fibrillation. Nat Commun 2019;10:1307.
13. Ramos KS, Brundel B. DNA damage, an innocent bystander in atrial fibrillation and other cardiovascular diseases? Front Cardiovasc Med 2020;7:67.
14. Collins AR. The comet assay for DNA damage and repair: principles, applications, and limitations. Mol Biotechnol 2004;26:249–261.
15. Mah LJ, El-Osta A, Karagiannis TC. gammaH2AX: a sensitive molecular marker of DNA damage and repair. Leukemia 2010;24:679–686.
16. Cheng KC, Cahill DS, Kasai H, Nishimura S, Loeb LA. 8-Hydroxyguanine, an abundant form of oxidative DNA damage, causes G—T and A—C substitutions. J Biol Chem 1992;267:166–172.
17. Ermakov AV, Konkova MS, Kostyuk SV, Izevskaya VL, Baranova A, Veiko NN. Oxidized extracellular DNA as a stress signal in human cells. Oxid Med Cell Longev 2013;2013:649747.
18. Zakkar M, Ascione R, James AF, Angelini GD, Suleiman MS. Inflammation, oxidative stress and postoperative atrial fibrillation in cardiac surgery. Pharmacol Ther 2015;154:13–20.
19. Petersen F, Rodrigo R, Richter M, Kostin S. The effects of polyunsaturated fatty acids and antioxidant vitamins on atrial oxidative stress, nitrotyrosine residues, and connexins following extracorporeal circulation in patients undergoing cardiac surgery. Mol Cell Biochem 2017;433:27–40.
20. Hussein AA, Bartz TM, Gottdiener JS, et al. Serial measures of cardiac troponin T levels by a highly sensitive assay and incident atrial fibrillation in a prospective cohort of ambulatory older adults. Heart Rhythm 2015;12:879–885.
21. Lippi G, Picanza A, Formentini A, Bonfanti L, Cervellin G. The concentration of troponin I is increased in patients with acute-onset atrial fibrillation. Int J Cardiol 2014;173:579–580.
22. Sorensen NA, Shah AS, Ojeda FM, et al. High-sensitivity troponin and novel biomarkers for the early diagnosis of non-ST-segment elevation myocardial infarction in patients with atrial fibrillation. Eur Heart J Acute Cardiovasc Care 2016;5:419–427.
23. Kumarathurai P, Mouridsen MR, Mattsson N, et al. Atrial ectopy and N-terminal pro-B-type natriuretic peptide as predictors of atrial fibrillation: a population-based cohort study. Europace 2017;19:364–370.
24. Kim SK, Park JH, Kim JY, et al. High plasma concentrations of transforming growth factor-beta and tissue inhibitor of metalloproteinase-1: potential non-invasive predictors for electroanatomical remodeling of atrium in patients with non-valvular atrial fibrillation. Circ J 2011;75:557–564.
25. Ardhianto P, Yuniadi Y. Biomarkers of atrial fibrillation: which one is a true marker? Cardiol Res Pract 2019;2019:8302326.
26. Toyama K, Yamabe H, Uemura T, et al. Analysis of oxidative stress expressed by urinary level of 8-hydroxy-2′-deoxyguanosine and biopyrrin in atrial fibrillation: effect of sinus rhythm restoration. Int J Cardiol 2013;168:80–85.
27. Dobrev D, Aguilar M, Heijman J, Guichard JB, Nattel S. Postoperative atrial fibrillation: mechanisms, manifestations and management. Nat Rev Cardiol 2019;16:417–436.
28. Ucar HI, Tok M, Atalar E, et al. Predictive significance of plasma levels of interleukin-6 and high-sensitivity C-reactive protein in atrial fibrillation after coronary artery bypass surgery. Heart Surg Forum 2007;10:E131–E135.
29. Nesher N, Frolkis I, Vardi M, et al. Higher levels of serum cytokines and myocardial tissue markers during on-pump versus off-pump coronary artery bypass surgery. J Card Surg 2006;21:395–402.
30. Wang M, Baker L, Tsai BM, Meldrum KK, Meldrum DR. Sex differences in the myocardial inflammatory response to ischemia-reperfusion injury. Am J Physiol Endocrinol Metab 2005;288:E321–E326.
31. Montaigne D, Marechal X, Lefebvre P, et al. Mitochondrial dysfunction as an arrhythmogenic substrate: a translational proof-of-concept study in patients with metabolic syndrome in whom post-operative atrial fibrillation develops. J Am Coll Cardiol 2013;62:1466–1473.
32. Kim YM, Guzik TJ, Zhang YH, et al. A myocardial Nox2 containing NAD(P)H oxidase contributes to oxidative stress in human atrial fibrillation. Circ Res 2005;97:629–636.