Atrial heat shock protein levels are associated with early postoperative and persistence of atrial fibrillation

Denise M.S. van Marion, MSc,* Kennedy S. Ramos, MD,*† Eva A.H. Lanters, MD,† Luciënne Baks-te Bulte, MSc,* Ad J.J.C. Bogers, MD, PhD,‡ Natasja M.S. de Groot, MD, PhD,† Bianca J.J.M. Brundel, PhD*

*From the *Department of Physiology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Amsterdam, The Netherlands, †Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands, and ‡Department of Cardiothoracic Surgery, Erasmus Medical Center, Rotterdam, The Netherlands.*

BACKGROUND Early detection and staging of atrial fibrillation (AF) is of importance for clinical management. Serum (bio)markers, such as heat shock proteins (HSP), may enable AF staging and identify patients at risk for AF recurrence and postoperative AF (PoAF).

OBJECTIVE This study evaluates the relation between serum and atrial tissue HSP levels, stages of AF, AF recurrence after treatment, and PoAF from patients undergoing cardiothoracic surgery.

METHODS Patients without (control) and with paroxysmal, persistent (PerAF), or longstanding persistent (LSPerAF) AF were included. HSPB1, HSPA1, HSPB7, and HSPD1 levels were measured in serum obtained prior to and post intervention. HSPB1, HSPA1, HSPA5, HSPD1, HSPB5, and pHSF1 levels were measured in left and/or right atrial appendages (respectively, LAA and RAA).

RESULTS In RAA, HSPA5 levels were significantly lower in LSPerAF and HSPD1 levels significantly higher in PerAF patients compared to controls. In RAA of controls who developed PoAF, HSPA1 and HSPA5 levels were significantly higher compared to those without PoAF. Also, HSPB1 RAA levels were lower and HSPA5 LAA levels higher in patients undergoing arrhythmia surgery who developed AF recurrence within 1 week after surgery compared to patients who did not.

CONCLUSION HSPA5 RAA and HSPD1 RAA and LAA levels are altered in persistent stages of AF. RAA HSPA1 and HSPA5 levels associate with development of PoAF. Additionally, HSPB1 RAA and HSPA5 LAA levels can predict AF recurrence in patients who underwent arrhythmia surgery. Nevertheless, HSP levels in serum cannot discriminate AF stages from controls, nor predict PoAF or AF recurrence after treatment.

KEYWORDS Atrial fibrillation; Heat shock protein; AF recurrence; Postoperation AF; Markers; Arrhythmia surgery; Cardiothoracic surgery

(Heart Rhythm 2021;18:1790–1798)

Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia, with a rising prevalence owing to the aging population.[1] AF is associated with severe complications such as thromboembolic events, heart failure, cognitive impairment, and increased mortality.[2,3] Although AF initially presents short, self-terminating episodes, it often progresses into long-lasting episodes that are more difficult to reverse to sinus rhythm.[4] The progressive stages of AF are rooted in the structural remodeling, which promotes contractile dysfunction and impairment of electrical conduction in atrial myocardium.[5-8] Thus, early detection and staging of AF and subsequent selection of appropriate treatment of AF is of utmost importance. Accordingly, there is an urgent need to identify diagnostic markers to aid patient-tailored therapy in order to treat this arrhythmia and to prevent its progression.

Markers are widely accepted as a diagnostic tool to screen or monitor patients for a variety of cardiovascular diseases. At present, several blood-based markers related to AF pathology have been identified, including brain natriuretic peptides,[9] high-sensitive cardiac troponin I,[10] and interleukin-6[11]; however, none of these markers are efficiently able to detect AF or predict the stage of AF or AF recurrence after therapy.

Emerging evidence indicates that derailed proteostasis in cardiomyocytes may underlie AF structural remodeling.[5,6,12] Heat shock proteins (HSPs) play an important role in

Funding sources: This research was funded by the LSH-Impulse grant (2014-40-43100-98-008), Dutch Heart Foundation (2020-2020B003, 2013-2013T144 and 2013-2013T096), CVON-STW2016-14728 AFFIP, NWO-Vidi (2016-91717339 to NMSdG), and Medical Delta. Disclosures: The authors have no conflicts of interest to disclose. **Address reprint requests and correspondence:** Dr Bianca Brundel, Department of Physiology, Amsterdam UMC, De Boelelaan 1117, Amsterdam, The Netherlands. E-mail address: b.brundel@amsterdamumc.nl.

 https://doi.org/10.1016/j.hrthm.2021.06.1194

safeguarding cellular proteostasis—ie, protein expression, function, and degradation in cells.[5] HSPs are upregulated during stress and disease, including early stage of AF, especially via activation of the heat shock transcription factor-1 (pHSF1).[13] Among the small HSPs, HSPB1 seems to be remarkably important in chaperoning proteostasis of cardiomyocytes by stabilizing the contractile proteins and preventing degradation.[14-17] Interestingly, HSPB1 levels were found to be increased in atrial tissue (right [RAA] and left atrial appendage [LAA]) samples of patients with paroxysmal AF (ParAF); however, these levels get exhausted in patients with longstanding persistent AF (LSPerAF),[14] indicating that low RAA and LAA HSPB1 levels are associated with AF progression. Furthermore, lower HSPA1 tissue levels correlate with postoperative AF (PoAF) in patients who underwent coronary artery bypass grafting (CABG).[18] Also, low HSPB1 levels in serum from patients treated with ablative therapy predicted AF recurrence.[19]

Whether serum HSP levels represent markers to identify the stage of AF, and predict PoAF and AF recurrence after treatment, is unknown. The aim of the current study is to evaluate whether serum, RAA, and LAA levels of several HSP family members, including HSPA1, HSPA5, HSPB1, HSPB5, HSPB7, HSPD1, and pHSF1, associate with the stage of AF, and predict onset and recurrence of AF in patients undergoing elective cardiothoracic surgery.

Methods

Study population

Patients, with history of AF (n = 60): ParAF (<7 days of AF), persistent AF (PerAF; 7 days to 1 year of AF), or LSPerAF (>1 year of AF); or without (n = 64), scheduled for elective cardiothoracic surgery—CABG and/or mitral valve surgery and/or aortic valve surgery and/or first correction of a congenital heart defect (mostly atrial septal defects)—were enrolled in the HALT & REVERSE study[20] at the department of cardiology and cardiothoracic surgery of the Erasmus MC, Rotterdam, the Netherlands; see Supplementary Material (Supplemental Table 1) for further information.

Sampling

Blood samples and RAAs were obtained from all patients. Amputation of the LAA was performed in 27 AF patients. Analysis of serum, RAA, and LAA samples were described in the Supplementary Material (Supplemental Table 2).

Statistical analysis

Details of statistical analysis are depicted in the Supplementary Material.

Results

Study population

The entire study population consisted of 124 patients (73.4 % male, aged 67.7 ± 10.6 years), including a control group of 64 (51.6 %) patients without AF and a study group of 60 patients with either ParAF (n = 15, 12.1 %), PerAF (n = 28, 22.6 %), or LSPerAF (n = 17, 13.7 %). Supplemental Table 1 outlines baseline characteristics of the entire study population.

The parameters age, sex, body mass index, hypertension, diabetes mellitus, dyslipidemia, thyroid disease, and left ventricular function were similar among the control and AF group.

AF patients more often use statins ($P < .01$ for PerAF, $P < .05$ for all patients with history of AF). Also, 63.3 % of the AF patients underwent arrhythmia surgery on top of the treatment for underlying heart disease. The type of underlying heart disease varies between control and AF group ($P < .001$).

HSP levels in atrial tissue (RAA and LAA) and serum related to clinical stage of AF

Serum RAA and LAA HSP levels were evaluated in relation to the degree of AF persistence. Atrial tissue (RAA and LAA) levels of HSPB1, HSPA1, HSPB5, and pHSF1 are similar between control and AF subgroups (Figure 1A, 1B, 1E, and 1F and Supplemental Table 3). HSPA5 levels in RAA are significantly lower in LSPerAF and in the total AF group (all patients with history of AF) when compared to control (Figure 1C and Supplemental Table 3). HSPD1 RAA levels are significantly higher in PerAF and in the total AF group compared to control. Also, LAA HSPD1 levels are significantly higher in PerAF compared to ParAF ($P < .05$) (Figure 1D and Supplemental Table 3). Western blot data for HSPD1 were comparable to ELISA data (Supplemental Table 4, Supplemental Figure 1). RAA and LAA levels are significantly positively correlated for HSPB1, HSPA1, HSPD1, and HSPB5 (Figure 2A, 2B, 2D, and 2E) while this was not the case for HSPA5 and pHSF1, the latest following an inverse line (Figure 2C and 2F). All original blots are presented in Supplemental Figures 2, 3, and 4.

Baseline HSPB1, HSPA1, HSPB7, and HSPD1 levels were determined in serum samples of ParAF, PerAF, and LSPerAF patients and compared to controls. Figure 3 shows similar baseline concentrations of serum HSPB1, HSPA1, HSPB7, and HSPD1 for control and AF patients (Supplemental Table 5). So, the findings indicate that RAA HSPA5 and RAA and LAA HSPD1 levels are associated with more persistent stages of AF and serum levels cannot be used to stage AF.

Association between HSP levels in atrial tissue and serum with development of PoAF

In the control group, 29 (45.3 %) of the patients developed PoAF. Figure 4 displays RAA samples HSP levels, serum HSP levels at baseline, and the levels of HSPB1 and HSPA1 in follow-up serum samples by comparing no-PoAF to de novo PoAF in controls (Supplemental Table 6). HSPA1 and HSPA5 RAA levels are significantly higher in

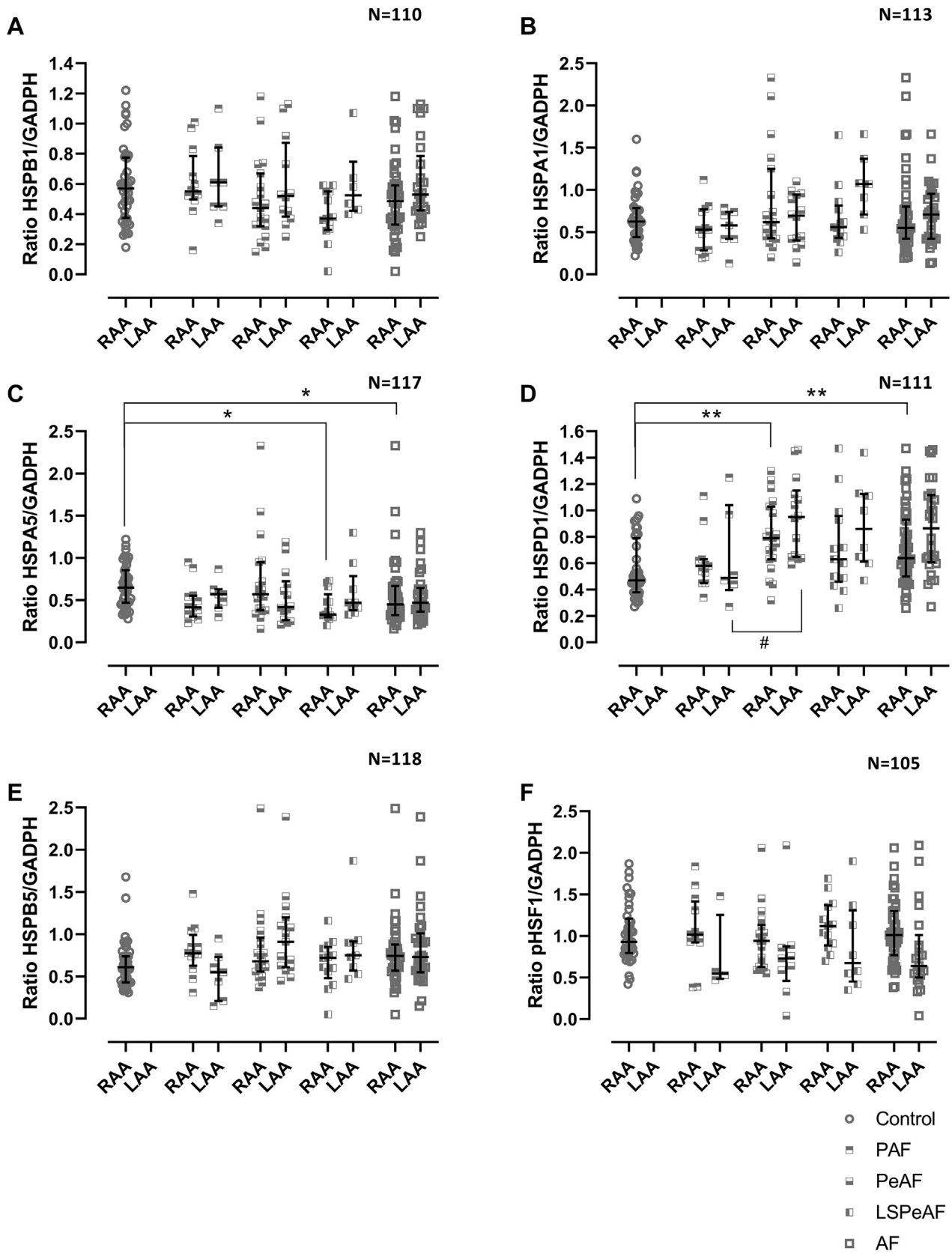

Figure 1 Heat shock protein (HSP) atrial tissue (right [RAA] and left atrial appendage [LAA]) levels from patients without and with history of atrial fibrillation (AF). Levels of HSPB1 (**A**), HSPA1 (**B**), HSPB5 (**E**), and pHSF1 (**F**) are similar between control and different stages of AF. **C:** HSPA5 levels in RAA are significantly lower in longstanding persistent AF (LSPerAF) ($P = .010$) and in the total AF group ($P = .013$) when compared with controls. **D:** HSPD1 levels in RAA are significantly higher in persistent AF (PerAF) ($P = .005$) and in the group of patients with any history of AF ($P = .003$) compared to control; also, HSPD1 levels in LAA are significantly higher in PerAF compared to paroxysmal AF (ParAF) ($P = .05$). *$P < .05$, **$P < .01$ vs groups as indicated. Statistical tests used: *t* test for control vs total AF and 1-way ANOVA with Bonferroni correction for control vs type AF on log-transformed values.

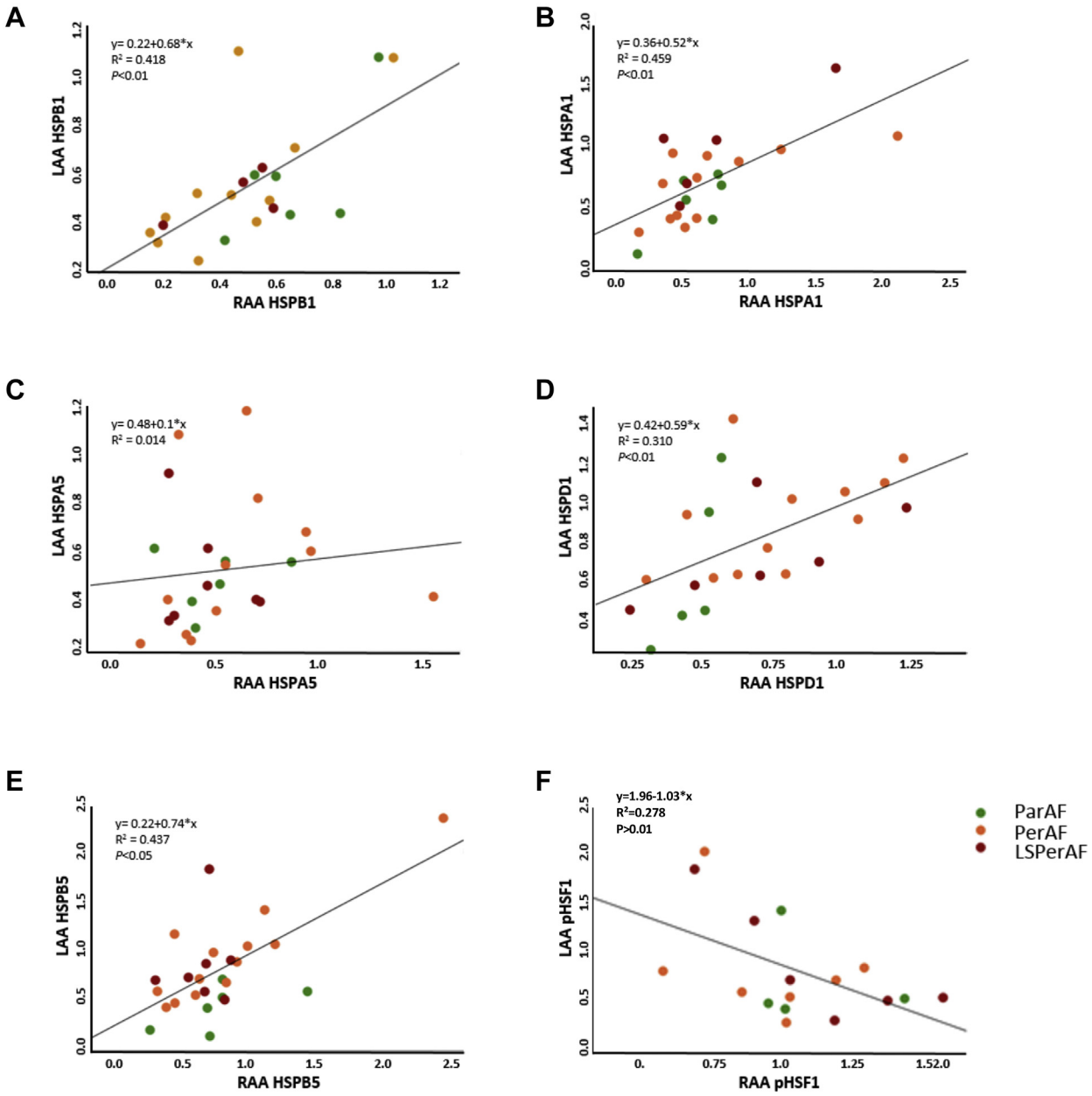

Figure 2 Correlations between left atrial appendage (LAA) and right atrial appendage (RAA) heat shock protein (HSP) levels. RAA and LAA levels are significantly correlated for HSPB1 ($P = .0011$) (**A**), HSPA1 ($P = .00013$) (**B**), HSPD1 ($P = .0011$) (**D**), HSPB5 ($P = .0077$) (**E**), and PHSF1 ($P = .014$) (**F**). No significant correlation was found for HSPA5 (**C**) and pHSF1 (**F**). Statistical tests used: Pearson correlation test on log values.

patients who developed PoAF compared to patients without PoAF (Figure 4A). HSPB1, HSPD1, HSPB5, and pHSF1 RAA levels were similar between PoAF and no-PoAF (Figure 4A).

Baseline serum HSPB1, HSPA1, HSPB7, and HSPD1 levels were similar between PoAF and no-PoAF in controls (Figure 4B). In addition, HSPB1 and HSPA1 levels at 6 and 12 months after surgery, relative to baseline levels and corrected for repeated measures, were comparable between the PoAF and no-PoAF groups (Figure 4C and D). These findings suggest that RAA tissue HSPA1 and HSPA5 associate with PoAF whereas serum levels do not.

Association between HSP levels in atrial tissue and serum with AF recurrence after arrhythmia surgery

We studied AF recurrences in patients treated for AF with arrhythmia surgery (Figure 5 and Supplemental Table 7). HSPA1, HSPA5, HSPD1, HSPB5, and pHSF1 RAA levels are similar between patients with and without AF recurrence after arrhythmia surgery. HSPB1 RAA levels are significantly lower in patients who developed AF recurrence (n = 15, from which 13.3 % are ParAF patients, 53.3 % are PerAF patients, and 33.3 % are LSPerAF patients) compared to patients without AF recurrence (n = 12, from which 41.6 % are ParAF patients, 33.3 % are PerAF patients, and 25 % are

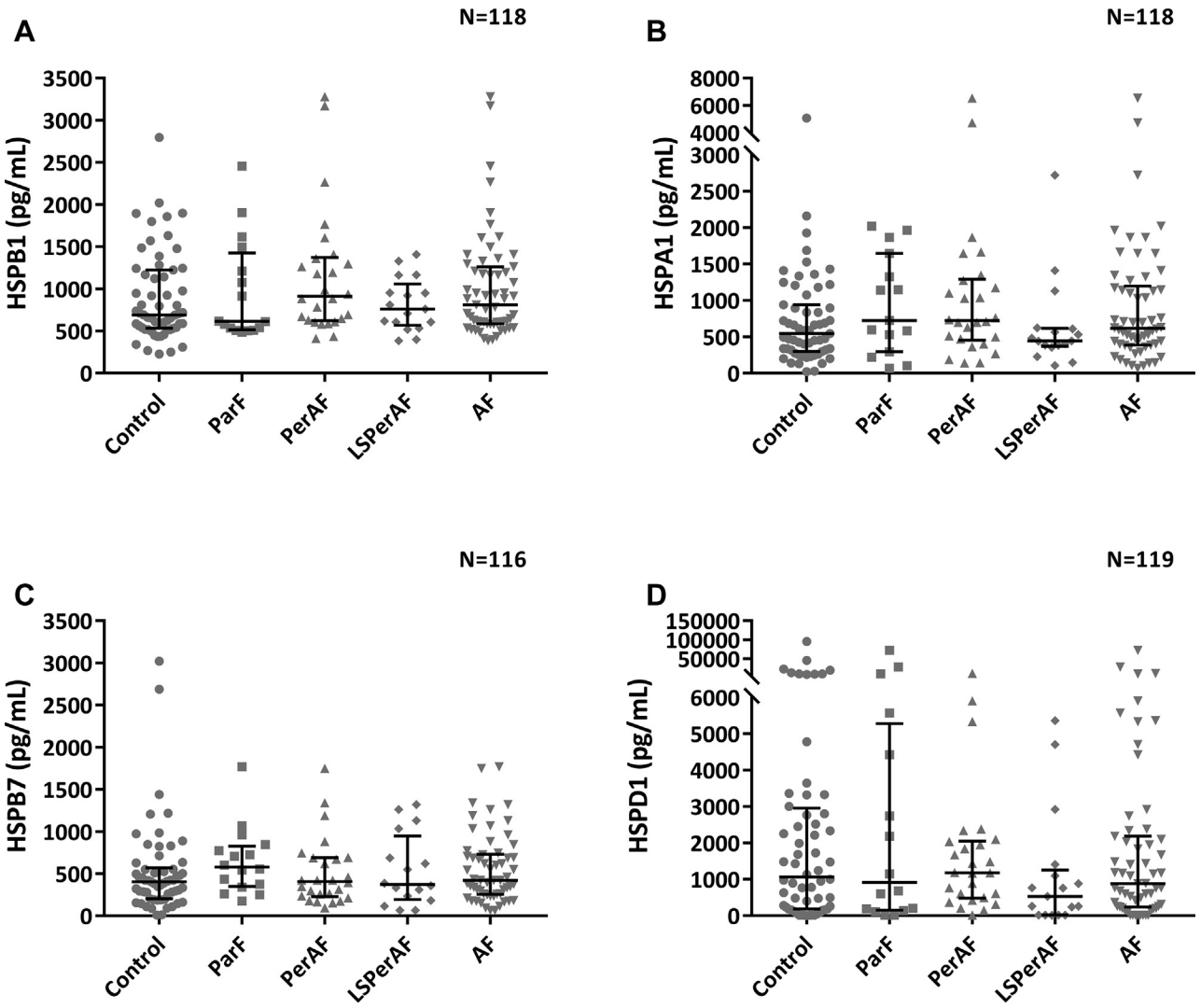

Figure 3 Baseline heat shock proteins (HSP) levels in patients without and with (ParAF, PerAF and LSPerAF) history of atrial fibrillation (AF). Serum levels of HSPB1 (**A**), HSPA1 (**B**), HSPB7 (**C**), and HSPD1 (**D**) are comparable between control and different stages of AF. Statistical tests used: *t* test for control vs total AF and 1-way ANOVA with Bonferroni correction for control vs type AF on log-transformed values.

LSPerAF patients), as depicted in Figure 5A, while this was not the case for LAA (Figure 5B). However, HSPA5 LAA levels were significantly higher in patients who developed AF recurrence (n = 13, from which 7.69 % are ParAF patients, 53.85 % are PerAF, and 38.46 % are LSPerAF) compared to patients without AF recurrence (n = 14, from which 42.86 % are ParAF, 42.86 % are PerAF, and 14.29 % are LSPerAF), as depicted in Figure 5B. This observation suggests that HSPB1 RAA levels and HSPA5 LAA levels may have value to predict AF recurrence.

No differences in baseline serum HSPB1, HSPA1, HSPB7, and HSPD1 levels were observed between patients with and without AF recurrence (Figure 5C). HSPB1 and HSPA1 levels at 6 and 12 months after surgery were similar between patients with and without AF recurrence relative to baseline levels and corrected for repeated measures (Figure 5D and 5E).

Discussion

In this study, we observed that atrial tissue (RAA and LAA) levels of HSPB1, HSPA1, HSPB5, and pHSF1 were similar in control patients and patients with paroxysmal and (long-standing) persistent AF. However, HSPA5 levels in RAA were significantly lower in LSPerAF and HSPD1 RAA levels higher in PerAF compared to controls, indicating an association with more persistent stages of AF. Serum HSPB1, HSPA1, HSPB7, and HSPD1 levels were not associated with AF. In control patients, HSPA1 and HSPA5 levels in RAA were significantly higher in patients who developed PoAF compared to patients who did not. However, neither baseline HSPB1, HSPA1, HSPB7, and HSPD1 serum levels nor HSPB1 and HSPA1 levels at 6 and 12 months after surgery could discriminate between no-PoAF and PoAF. In AF patients undergoing arrhythmia surgery, HSPB1 levels in RAA were lower and HSPA5 LAA levels higher in those

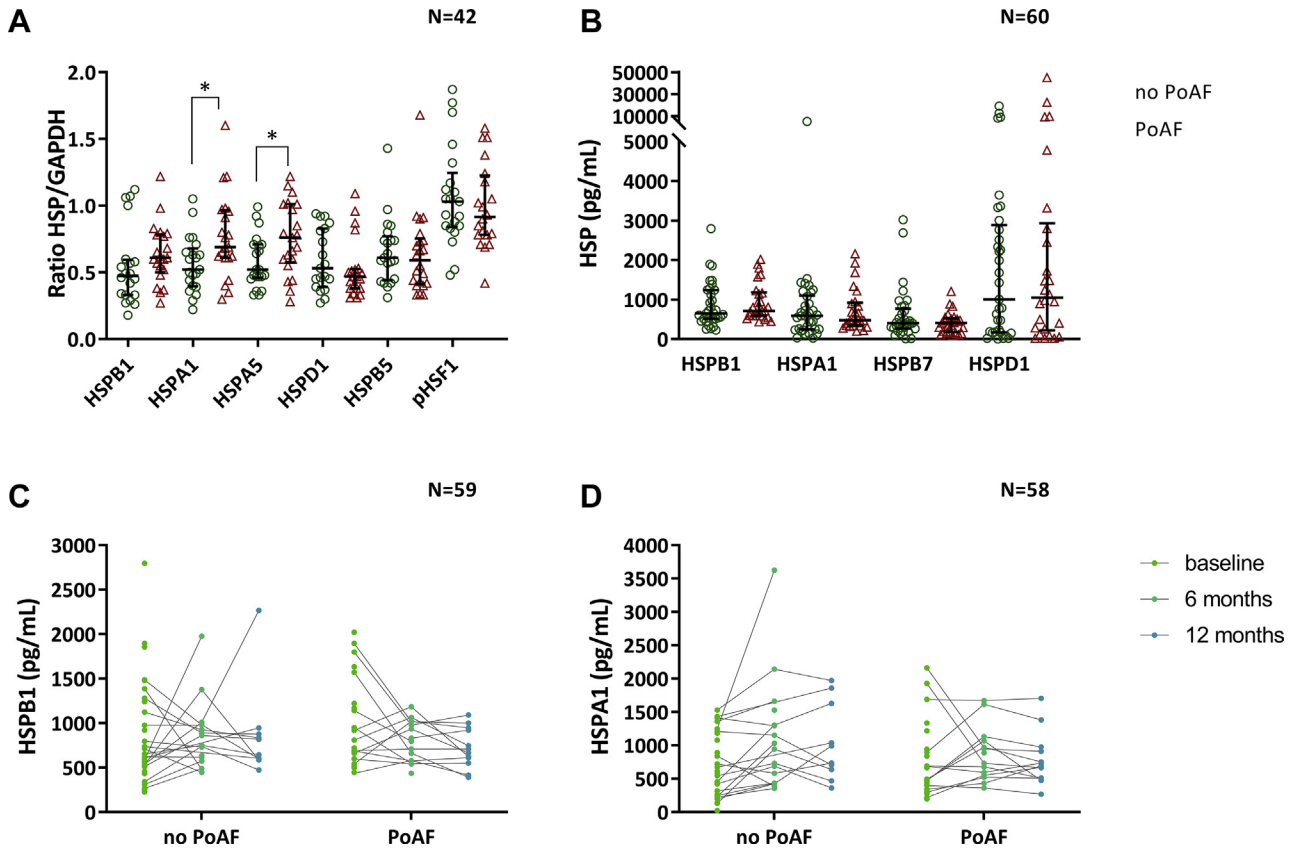

Figure 4 Relationship between heat shock proteins (HSP) levels in right atrial appendage (RAA) tissue and serum HSP levels regarding, with development of postoperative atrial fibrillation (PoAF). In RAA samples, HSPA1 ($P = .003$) and HSPA5 ($P = .03$) levels showed significant increase by comparing no PoAF to PoAF (**A**). Serum levels were similar between PoAF and no-PoAF for all HSPs (**B**), and between baseline and follow-up regarding HSPB1 and HSPA1 (**C, D**). Statistical tests used: **A, B:** *t* test for control vs total AF and 1-way ANOVA with Bonferroni correction for control vs type AF on log-transformed values. **C, D:** Correlation with serum HSP in time: repeated measures model ANOVA on log-transformed values.

patients who developed AF recurrence shortly after arrhythmia surgery compared to patients who did not. Baseline HSPB1, HSPA1, HSPB7, and HSPD1 serum levels and HSPB1 and HSPA1 serum levels in follow-up samples were similar between patients with and without AF recurrence.

In conclusion, findings of the current study suggest (1) RAA HSPA5, LAA, and RAA HSPD1 levels may have value to discriminate persistent AF from controls; (2) HSPA1 and HSPA5 RAA levels indicate PoAF in control patients; and (3) HSPB1 RAA levels and HSPA5 LAA levels indicate AF recurrence in patients undergoing arrhythmia surgery.

HSPs as a potential marker to stage AF

There is a great need for markers to detect and stage AF to subsequently start patient-tailored therapy. Despite the fact that several blood-based markers are routinely measured in clinical practice, they lack in sufficient specificity for AF. Similar to our previous study in AF patients treated with electrocardioversion and ablative therapy, no role for serum HSPB1, HSPA1, HSPB7, or HSPD1 levels to stage AF in patients undergoing cardiac surgery was found. For HSPA1, this is in line with other studies.[19,21] Yet, for HSPB1, our findings are in contrast to findings in the report of Hu et al.[19] Serum HSPB1 levels were found to be associated with history of AF, as HSPB1 levels were reduced in ParAF and LSPerAF patients compared to controls in sinus rhythm.[19] For HSPD1, no association between its serum levels and history of AF was found by Maan et al.[22] However, Cao et al[23] described that patients undergoing mitral valve replacement with AF revealed higher plasma HSPD1 levels compared to patients in sinus rhythm. No previous studies, except for our recent study,[24] investigated serum HSPB7 as a marker to stage AF.

Previous studies revealed an increase in HSPB1 levels[24] and HSPA1 levels[21] in follow-up serum samples of patients who developed AF recurrence post ablative therapy. Such an increase in HSPs in follow-up serum samples was not observed in the current study, which may be owing to presence of underlying heart diseases. Here, RAA levels of HSPA5 as well as both RAA and LAA HSPD1 levels may have value to indicate more persistent stages of AF. Lower RAA levels of the endoplasmic reticulum (ER) chaperone protein HSPA5 correlates with LSPerAF, and its values are increased in RAA of control patients with PoAF and in LAA of AF patients showing AF recurrence. These

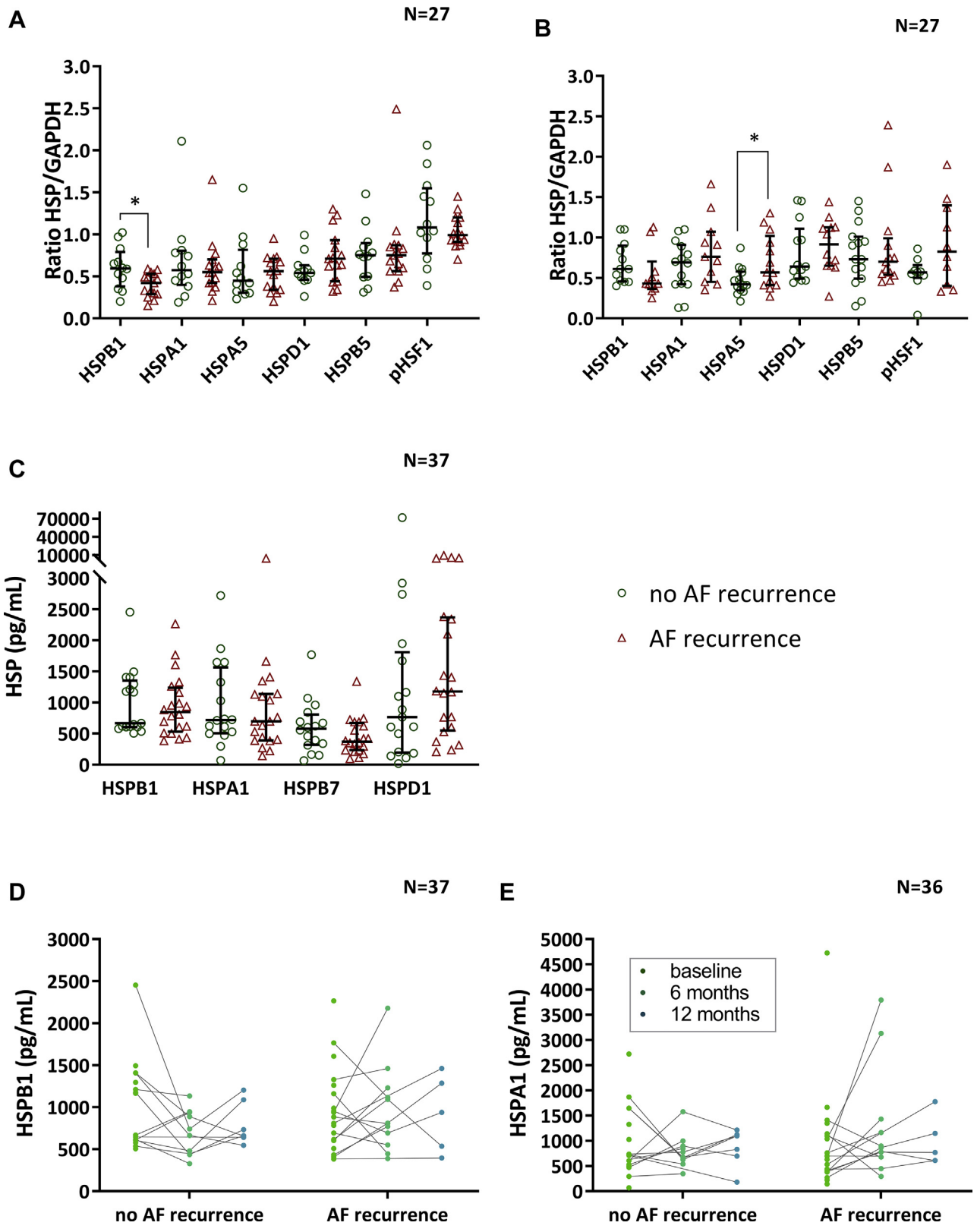

Figure 5 Atrial fibrillation (AF) recurrences after arrhythmia surgery. **A:** In right atrial appendage (RAA) only HSPB1 levels are significantly lower in patients who developed AF recurrence compared to patients without AF recurrence ($P = .013$). **B:** In left atrial appendage (LAA), only HSPA5 levels showed a significant increase in patients with AF recurrence ($P = .036$). **C:** Comparable levels of baseline serum from all HSPs were observed between patients with and without AF recurrence. **D, E:** HSPB1 and HSPA1 levels at 6 and 12 months after surgery were similar between patients with and without AF recurrence relative to baseline levels and corrected for repeated measures. *$P < .05$ vs group as indicated. Statistical tests used: *t* test for control vs total AF and 1-way ANOVA with Bonferroni correction for control vs type AF on log-transformed values.

findings suggest a role for ER stress to contribute to AF onset. Previously, Wiersma et al[6] showed induction of HSPA5 expression to attenuate AF-induced ER stress and downstream excessive activation of autophagic protein degradation pathway as protective mechanism against AF promotion. In line, higher levels of HSPA5, as observed in patients with PoAF and AF recurrence after arrhythmia surgery, may indicate the presence of ER stress and activation of compensatory mechanisms. In LSPerAF patients, low intracellular levels of HSPA5 may indicate exhaustion of the ER chaperone, ER stress, and autophagic protein degradation. Regarding the mitochondrial stress marker HSPD1, previous findings have shown higher mitochondrial stress markers in more persistent stages of AF, suggesting a role for mitochondria in AF.[25] The mitochondrial HSPs, HSPD1 and HSPE1, were more than doubled in the atrial myocardium of patients with persistent AF compared to control patients who underwent CABG and/or valve surgery.[26,27] Higher HSPD1 levels in patients with AF were confirmed in the study of Cao et al.[23] In the same study, HSPB1, HSPA1, and HSF1 tissue levels were lower in patients with AF, compared to patients without history of AF.[23] Other studies found HSPB1 levels to be increased in ParAF in comparison with patients in sinus rhythm and PerAF[14,28]; however, such an increase was not found for HSPA1. While our findings for HSPB1, HSPA1, HSPA5, HSPB5, and pHSF1 are not reaching consensus with all other reports, HSPD1 RAA and LAA levels are indicative for more persistent stages of AF in combination with underlying heart diseases. Interestingly, studies have shown influence of statins modulating HSP expression; nevertheless, we did observe similar serum HSPB1, HSPA1, HSPB7, and HSPD1 expression between AF groups (higher intake of statins) and control.

HSPs as marker for PoAF

Baseline HSPB1, HSPA1, HSPB7, and HSPD1 serum levels and follow-up HSPB1 and HSPA1 serum levels in control patients were not predictive for PoAF. For HSPA1, this finding is in accordance with other studies. In patients who underwent cardiac bypass surgery, baseline serum HSPA1 levels were also not predictive for PoAF[29,30] in contrast to another study, including 45 patients, showing higher pre- as well as postoperative circulating HSPA1 associated with PoAF.[31] Higher pre- and postoperative circulating anti-HSPD1 antibodies also associated with PoAF in patients who underwent cardiac bypass grafting.[32] Cao et al[23] also demonstrated that higher plasma HSPD1 levels were predictive for early (<7 days) PoAF.

Hereto, our findings of increased HSPA1 RAA levels in control patients with PoAF are not consistent with previous studies reporting significant correlation between low preoperative HSPA1 levels in tissue and high incidence of PoAF.[18,29] In contrast, the ER stress marker HSPA5 may help to predict PoAF in patients undergoing cardiac surgery.

HSP as marker for AF recurrence

Serum HSP levels in the current study could not predict AF recurrence in patients who underwent arrhythmia surgery. Previously, high serum HSPB1 was found to predict sinus rhythm maintenance after ablative therapy in the study of Hu et al.[19] While we observed an increase in follow-up serum HSPB1 levels in patients who developed AF recurrence post ablative therapy in our previous study,[24] Kornej et al[21] found increased serum HSPA1 levels at 6 months post ablative therapy to be correlated with AF recurrence, there was no such association between HSPB1 or HSPA1 levels after surgery, and AF recurrence was found in AF patients undergoing arrhythmia surgery. On the contrary, tissue levels of HSP may have value to predict AF recurrence after arrhythmia surgery in AF patients. Here we observed low levels of HSPB1 to associate with AF recurrence after arrhythmia surgery. This is in line with previous studies that have shown association between lower atrial HSPB1 levels and increased levels of structural remodeling (myolysis).[14] Possibly patients with AF recurrence may reveal more structural remodeling in comparison to patients presenting higher levels of HSPB1 and, consequently, low levels of structural remodeling. This suggests that these patients may present a culprit AF substrate, instead of a trigger originating from the pulmonary vein area. Furthermore, the higher levels of HSPA5 indicate ER stress. Additional research is warranted to elucidate the exact pathophysiological mechanisms underlying AF recurrence in these patients.

Limitations

No correlation between serum HSP levels and AF stage was observed; however, that does not negate a role for HSPs as a potential marker in AF. Since AF is a multifactorial disease and predisposing conditions for AF were omnipresent in both the AF and control group, serum HSPs might need to be correlated with more specific AF parameters, such as markers of structural damage that underlie atrial electrical conduction disorders.[5–8] It has been suggested that the clinical classification of AF is inaccurate for AF staging because it is not related to the degree of atrial conduction impairment, as measured by high-resolution epicardial mapping.[33] Since HSPs have been associated with structural remodeling,[12,14,17] future studies in larger-scale prospective trials with continuous rhythmic monitoring, including the rhythm at the moment of the surgery, and detection of HSP levels should elucidate the role of human HSP levels in both serum and atrial tissue in relation to AF. Since the pathophysiology of AF is complex and multifactorial, it may be helpful to combine HSP levels with other AF-related markers, such as cell-free-circulating mitochondrial DNA and DNA damage,[34,35] which may lift the diagnostic power of such a combination marker. We observed lower serum HSP27 and HSP70 ranges than the ranges described in other reports using Calbiochem, Stressgen, and Enzo Life Sciences kits. This can be explained by differences in the analytic assays used and disease status of the various patient groups.

Acknowledgments

The authors thank the atrial fibrillation innovation platform (AFIPonline.org) and all patients who participated in this study; A. Muskens, P. Knops, C.P. Teuwen, L.J.M.E. van der Does, and E.M.J.P. Mouws for their help with patient inclusion; and M. van Schaik and S. Martens for their help with Western blot and ELISA analyses.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.06.1194.

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. Circulation 2015;131:e29–e322.
2. Heijman J, Guichard JB, Dobrev D, Nattel S. Translational challenges in atrial fibrillation. Circ Res 2018;122:752–773.
3. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609–1678.
4. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369–2429.
5. Henning RH, Brundel B. Proteostasis in cardiac health and disease. Nat Rev Cardiol 2017;14:637–653.
6. Wiersma M, Meijering RAM, Qi XY, et al. Endoplasmic reticulum stress is associated with autophagy and cardiomyocyte remodeling in experimental and human atrial fibrillation. J Am Heart Assoc 2017;6.
7. 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.
8. Zhang D, Wu CT, Qi X, et al. Activation of histone deacetylase-6 induces contractile dysfunction through derailment of alpha-tubulin proteostasis in experimental and human atrial fibrillation. Circulation 2014;129:346–358.
9. Dudink EA, Weijs B, Tull S, et al. The biomarkers NT-proBNP and CA-125 are elevated in patients with idiopathic atrial fibrillation. J Atr Fibrillation 2018;11:2058.
10. Zhu K, Knuiman M, Divitini M, et al. High-sensitivity cardiac troponin I and risk of cardiovascular disease in an Australian population-based cohort. Heart 2018;104:895–903.
11. Stanciu AE, Vatasescu RG, Stanciu MM, Serdarevic N, Dorobantu M. The role of pro-fibrotic biomarkers in paroxysmal and persistent atrial fibrillation. Cytokine 2018;103:63–68.
12. Brundel BJ, Shiroshita-Takeshita A, Qi X, et al. Induction of heat shock response protects the heart against atrial fibrillation. Circ Res 2006;99:1394–1402.
13. Baler R, Dahl G, Voellmy R. Activation of human heat shock genes is accompanied by oligomerization, modification, and rapid translocation of heat shock transcription factor HSF1. Mol Cell Biol 1993;13:2486–2496.
14. Brundel BJ, Henning RH, Ke L, van Gelder IC, Crijns HJ, Kampinga HH. Heat shock protein upregulation protects against pacing-induced myolysis in HL-1 atrial myocytes and in human atrial fibrillation. J Mol Cell Cardiol 2006;41:555–562.
15. Kotter S, Unger A, Hamdani N, et al. Human myocytes are protected from titin aggregation-induced stiffening by small heat shock proteins. J Cell Biol 2014;204:187–202.
16. Ghosh JG, Houck SA, Clark JI. Interactive domains in the molecular chaperone human alphaB crystallin modulate microtubule assembly and disassembly. PLoS One 2007;2:e498.
17. Hu X, Li J, van Marion DMS, Zhang D, Brundel B. Heat shock protein inducer GGA*-59 reverses contractile and structural remodeling via restoration of the microtubule network in experimental atrial fibrillation. J Mol Cell Cardiol 2019;134:86–97.
18. St Rammos K, Koullias GJ, Hassan MO, et al. Low preoperative HSP70 atrial myocardial levels correlate significantly with high incidence of postoperative atrial fibrillation after cardiac surgery. Cardiovasc Surg 2002;10:228–232.
19. Hu YF, Yeh HI, Tsao HM, et al. Electrophysiological correlation and prognostic impact of heat shock protein 27 in atrial fibrillation. Circ Arrhythm Electrophysiol 2012;5:334–340.
20. Lanters EA, van Marion DM, Kik C, et al. HALT & REVERSE: Hsf1 activators lower cardiomyocyte damage; towards a novel approach to REVERSE atrial fibrillation. J Transl Med 2015;13:347.
21. Kornej J, Reinhardt C, Kosiuk J, et al. Response of circulating heat shock protein 70 and anti-heat shock protein 70 antibodies to catheter ablation of atrial fibrillation. J Transl Med 2013;11:49.
22. Maan A, Jorgensen NW, Mansour M, et al. Association between heat shock protein-60 and development of atrial fibrillation: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Pacing Clin Electrophysiol 2016;39:1373–1378.
23. Cao H, Xue L, Xu X, et al. Heat shock proteins in stabilization of spontaneously restored sinus rhythm in permanent atrial fibrillation patients after mitral valve surgery. Cell Stress Chaperones 2011;16:517–528.
24. Marion D, Lanters EAH, Ramos KS, et al. Evaluating serum heat shock protein levels as novel biomarkers for atrial fibrillation. Cells 2020;9:2105.
25. Wiersma M, van Marion DMS, Wust RCI, et al. Mitochondrial dysfunction underlies cardiomyocyte remodeling in experimental and clinical atrial fibrillation. Cells 2019;8:1202.
26. Schafler AE, Kirmanoglou K, Balbach J, Pecher P, Hannekum A, Schumacher B. The expression of heat shock protein 60 in myocardium of patients with chronic atrial fibrillation. Basic Res Cardiol 2002;97:258–261.
27. Schafler AE, Kirmanoglou K, Pecher P, Hannekum A, Schumacher B. Overexpression of heat shock protein 60/10 in myocardium of patients with chronic atrial fibrillation. Ann Thorac Surg 2002;74:767–770.
28. Yang M, Tan H, Cheng L, et al. Expression of heat shock proteins in myocardium of patients with atrial fibrillation. Cell Stress Chaperones 2007;12:142–150.
29. Mandal K, Torsney E, Poloniecki J, Camm AJ, Xu Q, Jahangiri M. Association of high intracellular, but not serum, heat shock protein 70 with postoperative atrial fibrillation. Ann Thorac Surg 2005;79:865–871. discussion 871.
30. Afzal AR, Mandal K, Nyamweya S, et al. Association of Met439Thr substitution in heat shock protein 70 gene with postoperative atrial fibrillation and serum HSP70 protein levels. Cardiology 2008;110:45–52.
31. Oc M, Ucar HI, Pinar A, et al. Heat shock protein 70: a new marker for subsequent atrial fibrillation development? Artif Organs 2008;32:846–850.
32. Oc M, Ucar HI, Pinar A, et al. Heat shock protein 60 antibody. A new marker for subsequent atrial fibrillation development. Saudi Med J 2007;28:844–847.
33. Mouws EMJP, van der Does LJME, Kik C, et al. Impact of the arrhythmogenic potential of long lines of conduction slowing at the pulmonary vein area. Heart Rhythm 2019;16:511–519.
34. Wiersma M, van Marion DMS, Bouman EJ, et al. Cell-free circulating mitochondrial DNA: a potential blood-based marker for atrial fibrillation. Cells 2020;9:1159.
35. Li J, Zhang D, Ramos KS, et al. Blood-based 8-hydroxy-2'-deoxyguanosine level: a potential diagnostic biomarker for atrial fibrillation. Heart Rhythm 2021;18:271–277.