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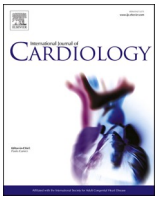

Dynamic biomarker profiles in patients with paroxysmal atrial fibrillation: Assessing the differences between sinus rhythm and acute atrial fibrillation episode

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ABSTRACT

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults, yet its underlying pathophysiology remains poorly understood. This study assessed whether circulating biomarker concentrations differ in paroxysmal AF patients during an acute episode compared to sinus rhythm.
Methods: The Time of Calamity study is a prospective biomarker study within the RACE V study. Patients underwent venous blood sampling in sinus rhythm at inclusion in RACE V, as well as during a subsequent acute episode of AF for which patients reported to the hospital. Ten biomarkers were analyzed.
Results: Thirty-nine patients (mean age 60 ± 9 years, 10 (25 %) women) were enrolled. During an acute AF episode, dickkopf-related protein 3 and insulin-like growth factor binding protein 7 were significantly lower, while N-terminal pro B-type natriuretic peptide (NT-proBNP), high-sensitive troponin T (hsTnT), growth differentiation factor 15, and interleukin 6 were significantly higher (all $p < 0.05$).
Conclusions: Biomarker concentrations in paroxysmal AF patients are dynamic and differ between sinus rhythm and acute AF episodes. Notably, NT-proBNP and hsTnT, commonly used in clinical practice, were significantly elevated during an acute AF episode.

1. Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in adults [1]. While it is thought that electrophysiological and structural abnormalities are fundamental in the development and persistence of AF [2], the exact pathophysiology of the disease is not fully understood. Biomarkers act as quantifiable markers of biological processes, and as such, analyzing biomarkers offers a way to evaluate the underlying mechanisms of the disease [3].

In the context of AF, biomarkers have demonstrated significant relevance. Various studies have examined biomarkers such as natriuretic peptides, inflammatory markers, and markers of myocardial injury, demonstrating their association with both prevalent and incident AF [4]. Additionally, biomarkers are thought to significantly enhance outcome prediction in AF, offering insights beyond traditional clinical risk factors for individuals with AF [5,6].

In the Time of Calamity (TOC) substudy of the Reappraisal of Atrial Fibrillation: Interaction between HyperCoagulability, Electrical remodelling, and Vascular Destabilisation in the Progression of AF (RACE V) study, we measured ten different biomarkers. These biomarkers were selected based on prior descriptions of their possible relation with AF [7]. To better understand the pathogenesis and key biomarkers of AF, we

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aimed to assess whether circulating biomarker concentrations differ in paroxysmal AF patients during an acute episode of AF compared to sinus rhythm.

2. Methods

2.1. Study design and population.

The TOC study is a prospective biomarker study within RACE V, which has previously been described [5,8]. In brief, the RACE V study is an ongoing investigator-initiated, prospective, Dutch multicenter observational study (Clinicaltrials.gov identifier NCT02726698) aiming to develop a clinical AF progression risk prediction model using extensive phenotyping and continuous rhythm monitoring in patients with paroxysmal AF [8]. They aimed to include 750 patients with a history of paroxysmal AF <10 years. Patients were eligible if they had ≥2 documented episodes of paroxysmal AF or one documented episode along with ≥2 symptomatic episodes suspected for AF; were willing to undergo implantation of a Medtronic (Minneapolis, USA) Reveal LINQ® implantable loop recorder; and did not have a history of persistent AF, (intention to undergo) pulmonary vein isolation or current amiodarone treatment. Patients with Medtronic pacemakers were also eligible if they had atrial high rate episodes (AHRE) exceeding 190 bpm for more than 6 min, as these were considered AF episodes. The study was performed in concordance with the Declaration of Helsinki and the institutional Review Board of all centers approved the protocol. We obtained written informed consent from all patients.

2.2. Study procedures.

At baseline, patients were extensively phenotyped [8]. Among others, clinical history, symptomatology, current medication, physical examination and 12-lead ECG were assessed. Besides, peripheral blood samples were taken whilst in sinus rhythm. As part of the TOC substudy, patients underwent one extra venous blood sampling during an acute episode of AF, for which patients reported to the hospital. The length of the AF episode was taken from the internal loop recorder or pacemaker and was defined as the period between AF onset and blood sampling.

2.3. Statistical analysis

Continuous variables with a normal distribution are shown as mean ± standard deviation, and those not normally distributed as median with interquartile range (IQR). Categorical variables are presented as frequencies and percentages. The concentrations of circulating biomarkers during the acute AF episode were compared to those at baseline in sinus rhythm using the Wilcoxon signed-rank test. Univariate linear regression analysis was performed to assess whether selected variables (chosen for their potential influence) other than the atrial rhythm status were linked to changes in serum biomarker levels. All statistical analysis were performed using IBM SPSS statistics for Windows, version 28 (IBM Corp., Armonk, NY). Two-sided p-values <0.05 were considered statistically significant.

3. Results

Thirty-nine patients were enrolled. The mean age was 60 ± 9 years, and 10 patients (25 %) were women. Median history of AF at baseline was 2.8 years (IQR: 0.8–5.7 years). Hypertension was present in 26 patients (67 %), diabetes mellitus in 3 patients (8 %), hypercholesterolemia in 21 patients (54 %) and coronary artery disease in 7 patients (18 %). Mean body mass index was 28 ± 5 kg/m^2. Mean systolic blood pressure at baseline was 134 ± 15 mmHg, and mean diastolic blood pressure was 80 ± 9 mmHg. Median time between baseline and TOC blood draw was 306 days (IQR: 97–620 days) and median duration of the acute ongoing episode of AF was 14 hours (IQR: 6–49 hours).

Comparison of circulating biomarker serum concentrations between sinus rhythm and AF showed that dickkopf-related protein 3 (DKK3) and insulin-like growth factor binding protein 7 (IGFBP7) were lower during AF, while N-terminal pro B-type natriuretic peptide (NT-proBNP), high-sensitive troponin T (hsTnT), growth differentiation factor 15 (GDF15) and interleukin 6 (IL6) were higher (Fig. 1). Univariate linear regression analysis revealed no associations between the mean or maximum ventricular rate of the AF episode, the duration of the AF episode, the time between baseline and TOC, AF burden preceding TOC and changes in serum biomarker levels (all $p > 0.05$). There were no major medication changes with regard to antiarrhythmic drugs or (serious) adverse events between baseline and TOC.

4. Discussion

In this study, we identified significant alterations in several biomarkers when comparing serum concentrations during an acute episode of AF to baseline measurements taken during sinus rhythm. The alterations in these biomarkers likely reflect the dynamic and complex pathophysiological state of the atria during an acute AF episode. The elevated levels of NT-proBNP, hsTnT and GDF15 indicate increased cardiac stress [9] and myocardial injury [9,10], highlighting the strain and damage the heart undergoes during AF. Additionally, the elevated levels of IL6 underscore the significant role of inflammation in the pathophysiology of AF, which is well-supported by extensive research [11]. Conversely, DKK3, a protein known for its cardioprotective properties against cardiac hypertrophy [12], was found to be decreased during an acute AF episode in our study. These results are in contrast to those of Staszewsky et al., which reported elevated DKK3 levels in patients with ongoing AF [13]. Similarly, our study revealed a decrease in IGFBP7 during AF, whereas Meessen et al. found higher concentrations of IGFBP7 associated with AF as compared to sinus rhythm [14]. The disparity in results could be attributed to variances in patient populations, with our study specifically focusing on individuals with paroxysmal AF.

Univariate linear regression analysis was conducted to determine if variables other than the atrial rhythm status were associated with changes in serum biomarker levels. The analysis found no links between the mean or maximum ventricular rate of the AF episode, the duration of the episode, the interval between baseline and TOC, or AF burden before TOC and changes in serum biomarker levels. Additionally, there were no significant changes in antiarrhythmic drugs or (serious) adverse events between baseline and TOC that could have impacted the biomarker levels. While our findings suggest that these biomarker changes result from the altered atrial state during AF, it is essential to recognize that these biomarkers may also play a role in precipitating AF episodes. Prior studies have indicated the potential predictive utility of several of these biomarkers, namely NT-proBNP, hsTnT, IL6, and GDF15 [9,15–18].

4.1. Strengths and limitations.

The key strength of this prospective study is its quasi-experimental design, which allows for the evaluation of changes in biomarker levels between sinus rhythm and an acute episode of AF. Moreover, the use of continuous rhythm monitoring allowed us to obtain accurate details regarding the length of the ongoing AF episode. However, there are also several limitations to consider. We included a relatively small sample size of patients, which limits the statistical power. Furthermore, there remains a possibility that other factors than the atrial rhythm status could have influenced the changes observed in biomarker values.

5. Conclusions

Based on our data, it can be concluded that biomarker concentrations are dynamic and differ between sinus rhythm and acute AF episodes in patients with paroxysmal AF. Notably, among the six biomarkers that

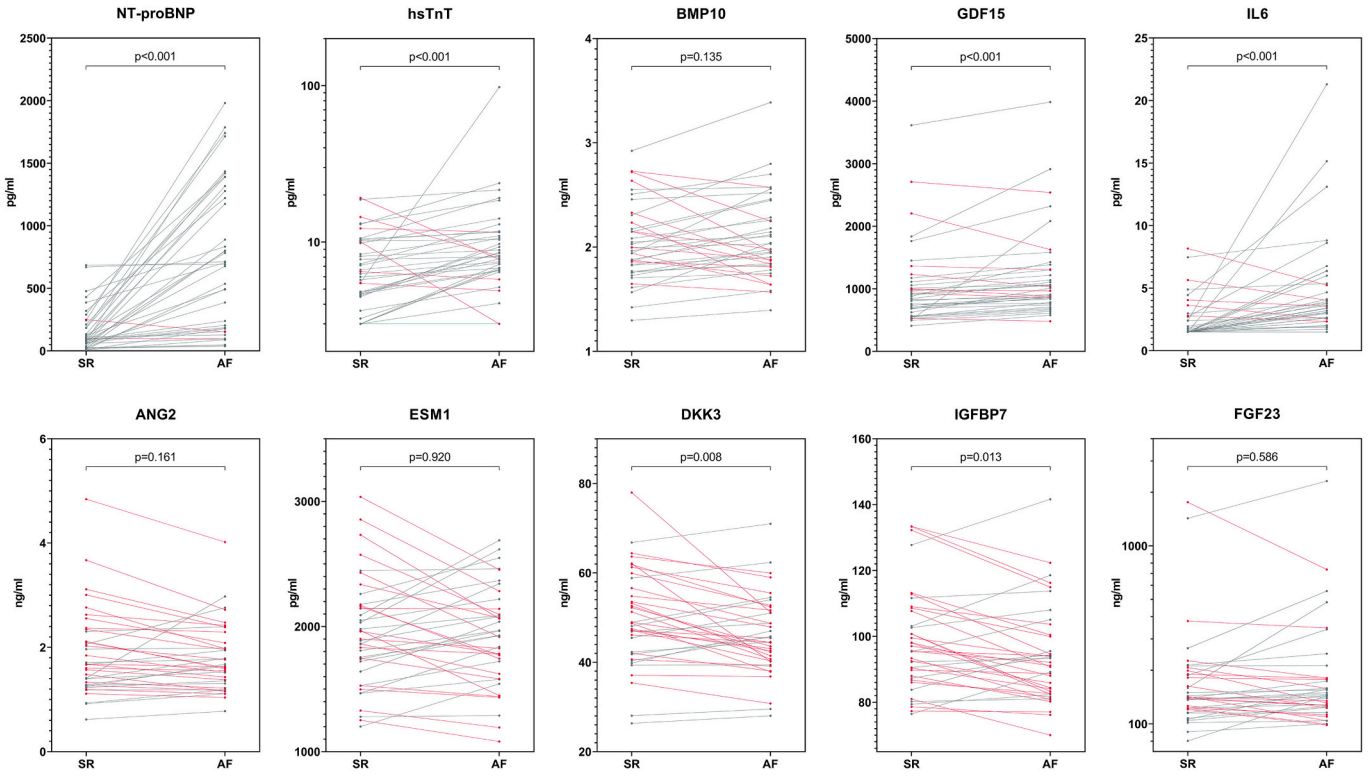

Fig. 1. Comparison of biomarker levels during sinus rhythm (SR; baseline) versus atrial fibrillation (AF; TOC) in patients with paroxysmal atrial fibrillation. NT-proBNP = N-terminal pro B-type natriuretic peptide; hsTnT = high-sensitive Troponin T; BMP10 = Bone Morphogenetic Protein 10; GDF15 = Growth Differentiation Factor 15; IL6 = Interleukin 6; ANG2 = Angiopoietin-2; ESM1 = Endothelial Cell Specific Molecule 1; DKK3 = Dickkopf-related protein 3; IGFBP7 = Insulin-like Growth Factor Binding Protein 7; FGF23 = Fibroblast Growth Factor 23.

changed during an acute AF episode, NT-proBNP and hsTnT, biomarkers frequently used in clinical practice, were significantly elevated. This elevation, observed even within a small sample size, may underscore robustness and reliability of NT-proBNP and hsTnT as indicators of acute cardiac stress and injury during an acute AF episode.

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Disclosures

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CRediT authorship contribution statement

Marieke J.H. Velt: Writing – original draft, Visualization, Validation, Formal analysis. **Harry J.G.M. Crijns:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Isabelle C. van Gelder:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Dominik Linz:** Writing – review & editing, Conceptualization. **Martijn E. van de Lande:** Writing – review & editing, Investigation, Data curation. **Hugo ten Cate:** Writing – review & editing, Conceptualization. **Henri M.H. Spronk:** Writing – review & editing, Conceptualization. **Mirko de Melis:** Writing – review & editing, Resources, Conceptualization. **Michiel Rienstra:** Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization. **Bart A. Mulder:** Writing – original draft, Validation, Supervision.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

[1] E.J. Benjamin, P. Muntner, A. Alonso, M.S. Bittencourt, C.W. Callaway, A. P. Carson, A.M. Chamberlain, A.R. Chang, S. Cheng, S.R. Das, F.N. Delling, L. Djousse, M.S.V. Elkind, J.F. Ferguson, M. Fornage, L.C. Jordan, S.S. Khan, B. M. Kissela, K.L. Knutson, T.W. Kwan, D.T. Lackland, T.T. Lewis, V.S. Lic, Heart

disease and stroke Statistics-2019 update: a report from the American Heart Association, Circulation 139 (2019) 56–528.
[2] J.A. Joglar, M.K. Chung, A.L. Armbruster, E.J. Benjamin, J.Y. Chyou, E.M. Cronin, et al., 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and Management of Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines, Circulation 149 (2024) E1–156, https://doi.org/10.1161/CIR.0000000000001193.
[3] A. Ahmad, M. Imran, H. Ahsan, Biomarkers as biomedical bioindicators: approaches and techniques for the detection, analysis, and validation of novel biomarkers of diseases, Pharmaceutics 15 (2023), https://doi.org/10.3390/PHARMACEUTICS15061630.
[4] P.B. Meyre, S. Aeschbacher, S. Blum, G. Voellmin, P.M. Kastner, E. Hennings, et al., Biomarkers associated with rhythm status after cardioversion in patients with atrial fibrillation, Sci. Rep. 12 (2022) 1680, https://doi.org/10.1038/S41598-022-05769-9.
[5] B.O. Nguyen, V. Weberndorfer, H.J.G.M. Crijns, B. Geelhoed, H. Ten Cate, H. Spronk, et al., Prevalence and determinants of atrial fibrillation progression in paroxysmal atrial fibrillation, Heart 109 (2022) 186–194, https://doi.org/10.1136/HEARTJNL-2022-321027.
[6] W.Y. Ding, G. Mcdowell, G.Y.H. Lip, Utilizing biomarkers in atrial fibrillation: the pros and cons, Cardiovasc. Res. 118 (2022) 2035–2036, https://doi.org/10.1093/CVR/CVAB283.
[7] E. Palà, B. Alejandro, J. Pagola, J. Juega, J. Francisco-Pascual, A. Penalba, et al., Blood-based biomarkers to search for atrial fibrillation in high-risk asymptomatic individuals and cryptogenic stroke patients, Front Cardiovasc Med 9 (2024).
[8] R.R. de With, Ö. Erküner, M. Rienstra, B.O. Nguyen, F.W.J. Körver, D. Linz, et al., Temporal patterns and short-term progression of paroxysmal atrial fibrillation: data from RACE V, Europace 22 (2020) 1162–1172, https://doi.org/10.1093/EUROPACE/EUAA123.
[9] B. Toprak, S. Brandt, J. Brederecke, F. Gianfagna, J.K.K. Vishram-Nielsen, F. M. Ojeda, et al., Exploring the incremental utility of circulating biomarkers for robust risk prediction of incident atrial fibrillation in European cohorts using regressions and modern machine learning methods, Europace 25 (2023) 812, https://doi.org/10.1093/EUROPACE/EUAC260.
[10] T. Kempf, M. Eden, J. Strelau, M. Naguib, C. Willenbockel, J. Tongers, et al., The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury, Circ. Res. 98 (2006) 351–360, https://doi.org/10.1161/01.RES.0000202805.73038.48.
[11] P. Korantzopoulos, K.P. Letsas, G. Tse, N. Fragakis, C.A. Goudis, T. Liu, Inflammation and atrial fibrillation: a comprehensive review, J Arrhythmia 34 (2018) 394, https://doi.org/10.1002/JOA3.12077.
[12] Y. Zhang, Y. Liu, X.H. Zhu, X.D. Zhang, D.S. Jiang, Z.Y. Bian, et al., Dickkopf-3 attenuates pressure overload-induced cardiac remodelling, Cardiovasc. Res. 102 (2014) 35–45, https://doi.org/10.1093/CVR/CVU004.
[13] L. Staszewsky, J.M.T.A. Meessen, D. Novelli, U.H. Wienhues-Thelen, M. Disertori, A.P. Maggioni, et al., Total NT-proBNP, a novel biomarker related to recurrent atrial fibrillation, BMC Cardiovasc. Disord. (2021) 21, https://doi.org/10.1186/S12872-021-02358-Y.
[14] J.M.T.A. Meessen, G. Cesaroni, G.F. Mureddu, A. Boccanelli, U.H. Wienhues-Thelen, P. Kastner, et al., IGFBP7 and GDF-15, but not P1NP, are associated with cardiac alterations and 10-year outcome in an elderly community-based study, BMC Cardiovasc. Disord. 21 (2021), https://doi.org/10.1186/S12872-021-02138-8.
[15] D. Dobrev, J. Heijman, R. Hiram, N. Li, S. Nattel, Inflammatory signalling in atrial cardiomyocytes: a novel unifying principle in atrial fibrillation pathophysiology, Nat. Rev. Cardiol. 20 (2023) 145, https://doi.org/10.1038/S41569-022-00759-W.
[16] K. Nakanishi, S. Fukuda, H. Yamashita, T. Hasegawa, M. Kosaka, N. Shirai, et al., High-sensitive cardiac troponin T as a novel predictor for recurrence of atrial fibrillation after radiofrequency catheter ablation, Europace 19 (2017) 1951–1957, https://doi.org/10.1093/EUROPACE/EUW314.
[17] M. Chen, N. Ding, Y. Mok, L. Mathews, R.C. Hoogeveen, C.M. Ballantyne, et al., Growth differentiation factor 15 and the subsequent risk of atrial fibrillation: the atherosclerosis risk in communities study, Clin. Chem. 68 (2022) 1084–1093, https://doi.org/10.1093/CLINCHEM/HVAC096.
[18] W. Chua, A. Khashaba, H. Canagarajah, J.C. Nielsen, L. di Biase, K.G. Haeusler, et al., Disturbed atrial metabolism, shear stress, and cardiac load contribute to atrial fibrillation after ablation: AXAFA biomolecule study, Europace 26 (2024), https://doi.org/10.1093/EUROPACE/EUAE028.