Clinical Significance of Skin Autofluorescence in Elderly Patients With Long-Standing Persistent Atrial Fibrillation

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Abstract

Background: Recent clinical studies have demonstrated the importance of skin autofluorescence as a cardiovascular risk factor. However, data regarding the relationship between skin autofluorescence and atrial fibrillation are limited. The aim of this study was to clarify the clinical significance of skin autofluorescence in elderly patients with long-standing persistent atrial fibrillation.

Methods: This cross-sectional study enrolled 112 elderly patients with long-standing persistent atrial fibrillation who were treated medically (46 men and 66 women; mean age, 81 ± 9 years). The association between skin autofluorescence and various clinical parameters was examined.

Results: Significant relationships were observed between skin autofluorescence and CHADS2 score (r = 0.53, P < 0.001), high-sensitivity cardiac troponin T level (r = 0.43, P < 0.001), reactive oxygen metabolite levels (r = 0.52, P < 0.001), and whole blood passage time (r = 0.45, P < 0.001). Furthermore, multiple regression analyses showed that these clinical parameters were independent variables when skin autofluorescence was used as a subordinate factor. Receiver-operating characteristic curve analysis indicated that the risk values of skin autofluorescence as a cardiovascular risk factor. How skin autofluorescence for high CHADS2 scores (≥ 2) or elevated high-sensitivity cardiac troponin T levels (> 0.014ng/mL) were 2.6 arbitrary units (AU) and 2.7 AU, respectively.

Conclusions: The findings of this study indicated that skin autofluorescence is significantly associated with other diseases such as ischemic stroke and heart failure [1]. In recent years, the prevalence of atrial fibrillation has increased because of a concomitant increase in life expectancy [2]. Treatment via an electrophysiologic catheter ablation procedure can be performed for selected patients with atrial fibrillation [3], which may achieve a complete cure in some. Catheter ablation is particularly useful in patients with paroxysmal atrial fibrillation, but less so in those with persistent atrial fibrillation [4, 5]. In addition, elderly patients with persistent atrial fibrillation are less likely to receive the procedure for various reasons such as duration of atrial fibrillation, symptoms, activities of daily practice, patient refusal, and limited procedural benefit.

Advanced glycation end products (AGEs) and receptors of AGEs play an important role in the pathophysiology of cardiovascular disease [6, 7]. Among the methods used to evaluate AGEs, skin autofluorescence is known to be a simple and reliable marker of AGEs in vivo, and recent clinical studies have indicated that skin autofluorescence is significantly associated with cardiovascular disease [8-10]. However, data regarding the relationship between skin autofluorescence and atrial fibrillation are limited. This cross-sectional study attempted to clarify the clinical significance of skin autofluorescence in elderly patients with long-standing persistent atrial fibrillation.

Materials and Methods

Patients

In this study, 112 elderly outpatients (age ≥ 65 years) with long-standing persistent atrial fibrillation who were being treated medically at the Hitsumoto Medical Clinic, Yamaguchi, Japan were enrolled between January 2017 and December 2018. Long-standing persistent atrial fibrillation (presence of atrial fibrillation for ≥1 year after initiation of rhythm control treatment) is defined by the 2010 Guidelines for the Management of Atrial Fibrillation of the European Society of Cardiology [11]. The patients included 46 (41%) men and 66 (59%) women. The mean patient age was 81 ± 9 years. The study was approved by the Institutional Review Board of the Hitsumoto Medical Clinic (approval number 2017-01) and was conducted in compliance with the Declaration of Helsinki. All patients provided informed consent.

Measurement of skin autofluorescence

Skin autofluorescence was measured using a commercial de-
Skin Autofluorescence and Atrial Fibrillation

Cardiol Res. 2019;10(3):181-187

Discussion

This study aimed to clarify the clinical significance of skin autofluorescence in elderly patients with long-standing persistent atrial fibrillation. The results showed an independent association between skin autofluorescence and CHADS2 score, whole blood passage time, hs-cTnT level, and d-ROMs test. In addition, the receiver-operating characteristic curve analysis indicated that the skin autofluorescence values associated with high CHADS2 scores and elevated hs-cTnT levels in this study population were > 2.6 AU and > 2.7 AU, respectively.

The CHADS2 score is a well-known predictor of ischemic stroke in patients with atrial fibrillation [15, 22]. Therefore, the
independent association between skin autofluorescence and the CHADS\_2 score in this study suggests that increased skin autofluorescence is closely associated with ischemic stroke in elderly patients with long-standing persistent atrial fibrillation; consequently, treatment directed at decreasing AGEs may prevent ischemic stroke by improving blood rheology.

Recent clinical studies have shown the clinical importance of hs-cTnT levels as a prognostic factor in patients with atrial fibrillation [23, 33]. In addition, hs-cTnT is used as a biomarker to clinically evaluate the severity of myocardial injury. Hofmann et al found a significant relationship between AGE-modified cardiac tissue collagen and skin autofluorescence [34]. They also showed that the AGE level found at the volar side of the forearm seemed to reflect the degree of AGE accumulation in cardiomyocytes. In addition, basic science studies have indicated that AGEs cause impaired blood rheology by mechanisms such as leukocyte-endothelial interaction, activation of platelet aggregation, and increased levels of plasminogen activator inhibitor-1 [30-32]. Therefore, the independent association between skin autofluorescence and whole blood passage time in this study can be explained by hypothesizing that AGEs play an important role in impairing blood rheology in elderly patients with long-standing persistent atrial fibrillation; consequently, treatment directed at decreasing AGEs may prevent ischemic stroke by improving blood rheology.

### Table 1. Patient Characteristics

| Parameter                          | Value               |
|------------------------------------|---------------------|
| n (male/female)                    | 112 (46/66)         |
| Age (years)                        | 81 ± 9              |
| Skin autofluorescence (AU)         | 2.8 ± 0.5           |
| CHADS\_2 score                     | 3 ± 2               |
| Body mass index (kg/m\^2)          | 22.6 ± 3.5          |
| Current smoker, n (%)              | 14 (13)             |
| Hypertension, n (%)                | 75 (67)             |
| Systolic blood pressure (mm Hg)    | 131 ± 11            |
| Diastolic blood pressure (mm Hg)   | 76 ± 9              |
| Dyslipidemia, n (%)                | 76 (68)             |
| Total cholesterol (mg/dL)          | 218 ± 41            |
| LDL cholesterol (mg/dL)            | 137 ± 37            |
| Triglyceride (mg/dL)               | 127 ± 66            |
| HDL cholesterol (mg/dL)            | 55 ± 15             |
| Diabetes mellitus, n (%)           | 30 (27)             |
| Fasting blood glucose (mg/dL)      | 104 ± 32            |
| Hemoglobin A\_1c (%)               | 5.9 ± 0.6           |
| IVSTd (mm)                         | 9.7 ± 2.2           |
| LVDd (mm)                          | 51.5 ± 5.9          |
| LVEF (%)                           | 64.4 ± 12.2         |
| LAD (mm)                           | 46.9 ± 6.8          |
| eGFR (mL/min/1.73m\^2 \_)          | 51.8 ± 19.1         |
| Log-BNP (pg/mL)                    | 2.3 ± 0.4           |
| Log-hs-cTnT (ng/mL)                | -1.8 ± 0.4          |
| d-ROMs test (U. CARR)              | 325 ± 82            |
| WBPT (s)                           | 59.5 ± 18.3         |
| Medication                         |                     |
| RAS inhibitor, n (%)               | 61 (55)             |
| β blocker, n (%)                   | 23 (21)             |
| Diuretics, n (%)                   | 31 (28)             |
| Statin, n (%)                      | 35 (31)             |
| Warfarin/DOAC, n (%)               | 33 (29)/79 (71)     |

Continuous values are mean ± SD. AU: arbitrary units; LDL: low-density lipoprotein; HDL: high-density lipoprotein; IVSTd: interventricular septal thickness at end-diastole; LVDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LAD: left atrial dimension; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; hs-cTnT: high sensitivity cardiac troponin T; d-ROMs: derivatives of reactive oxygen metabolites; WBPT: whole blood passage time; RAS: renin-angiotensin system; DOAC: direct oral anticoagulant.
shown a close association between AGEs or receptors of AGEs and oxidative stress in the heart and arterial vessels [24, 39, 40]. The results of this study also indicated that the d-ROMs test as an *in vivo* marker of oxidative stress is an important factor for skin autofluorescence. A previous study reported that increased activity of the renin-angiotensin system caused increased oxidative stress or AGE production, and the use of an angiotensin receptor blocker decreased both oxidative stress and receptors of AGEs [41]. This study showed a significantly negative association between angiotensin receptor blocker use and skin autofluorescence, even though angiotensin receptor blocker use was not selected in the multivariate model. Therefore, we have started to intervene by prescribing an angiotensin receptor blocker for patients with high skin autofluorescence; consequently, we expect a reduction in cardiovascular events, including ischemic stroke or heart failure, in elderly patients with long-standing persistent atrial fibrillation.

This study clarified the clinical usefulness of assessing skin autofluorescence to detect a high CHADS<sub>2</sub> score ≥ 2 or an elevated hs-cTnT level > 0.014 ng/mL, which are associated with cardiovascular events such as ischemic stroke, heart failure, and coronary artery disease in patients with atrial fibrillation according to previous reports. The receiver-operating characteristic curve analysis indicated that skin autofluorescence values > 2.6 AU and > 2.7 AU are the optimal cutoff points to identify a high CHADS<sub>2</sub> score and an elevated hs-cTnT level, respectively. Therefore, this study indicated that maintaining skin autofluorescence values ≤ 2.6 AU or ≤ 2.7 AU in elderly patients with long-standing persistent atrial fibrillation may decrease cardiovascular events. Genevieve et al performed a study regarding the association between skin autofluorescence and HbA1c levels in patients with diabetes mellitus, and reported that skin autofluorescence was significantly associated with the means of the last five and 10 HbA1c values [42]. In addition, Isami et al reported that lifestyle habits such as physical activity, nonsmoking, adequate sleep, low mental stress level, eating breakfast, and abstaining from sugary foods were independently associated with lower skin autofluorescence [43]. Therefore, it appears that long-term adequate blood glucose control and good lifestyle habits are important to maintain lower skin autofluorescence as early as possible.

**Limitations**

This study has several limitations. First, the various medical treatments may have affected the study results. Second, skin autofluorescence was measured in only Japanese patients; previous studies have indicated that skin autofluorescence varies according to race [44, 45]. Therefore, the cutoff values for skin autofluorescence found in this study may not apply to non-Japanese populations. Finally, the study design was a single-center cross-sectional study, and the sample size was relatively small. Additional prospective studies, including evaluations...
of interventional therapies, are required to clarify the clinical significance of skin autofluorescence in elderly patients with long-standing persistent atrial fibrillation.

Conclusions

In conclusion, the findings of this study showed that skin autofluorescence may be a prognostic factor in elderly patients with long-standing persistent atrial fibrillation. The risk value of skin autofluorescence was considered as 2.6 AU or 2.7 AU. Further prospective studies that include the evaluation of therapies are required to validate the results of this study.

Table 2. Relationship Between Skin Autofluorescence and Various Clinical Parameters

|                           | r    | P value |
|---------------------------|------|---------|
| Sex (female = 0, male = 1) | -0.14| 0.139   |
| Body mass index           | -0.13| 0.183   |
| Current smoker (no = 0, yes = 1) | 0.24  | 0.009   |
| Systolic blood pressure   | 0.02 | 0.852   |
| Diastolic blood pressure  | -0.03| 0.732   |
| Dyslipidemia (no = 0, yes = 1) | 0.02  | 0.852   |
| Total cholesterol         | 0.02 | 0.837   |
| LDL cholesterol           | 0.01 | 0.924   |
| Triglyceride              | 0.05 | 0.582   |
| HDL cholesterol           | -0.12| 0.190   |
| Fasting blood glucose     | 0.06 | 0.566   |
| Hemoglobin A1c            | 0.24 | 0.012   |
| IVSTd                     | 0.02 | 0.861   |
| LVDd                      | 0.08 | 0.319   |
| LVEF                      | 0.11 | 0.251   |
| LAD                       | 0.19 | 0.051   |
| eGFR                      | -0.37| < 0.001 |
| Log-BNP                   | 0.32 | < 0.001 |
| Log-hs-cTnT               | 0.43 | < 0.001 |
| d-ROMs test               | 0.52 | < 0.001 |
| WBPT                      | 0.45 | < 0.001 |
| RAS inhibitor (no = 0, yes = 1) | -0.16 | 0.048   |
| β blocker (no = 0, yes = 1) | 0.14  | 0.137   |
| Diuretics (no = 0, yes = 1) | 0.18  | 0.062   |
| Statin (no = 0, yes = 1)  | 0.09 | 0.351   |
| Anticoagulant (warfarin = 0, DOAC = 1) | -0.04 | 0.965   |

r expressed correlation coefficient. LDL: low-density lipoprotein; HDL: high-density lipoprotein; IVSTd: interventricular septal thickness at end-diastole; LVDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LAD: left atrial dimension; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; hs-cTnT: high sensitivity cardiac troponin T; IVSTd: interventricular septal thickness at end-diastole; d-ROMs: derivatives of reactive oxygen metabolites; WBPT: whole blood passage time; RAS: renin-angiotensin system; DOAC: direct oral anticoagulant.

Table 3. Multiple Regression Analysis for Skin Autofluorescence

| Explanatory factor | β     | P value |
|--------------------|-------|---------|
| CHADS2 score       | 0.33  | < 0.001 |
| WBPT               | 0.25  | 0.002   |
| d-ROMs test        | 0.21  | 0.019   |
| Log-hs-cTnT        | 0.19  | 0.020   |

R² = 0.47. WBPT: whole blood passage time; d-ROMs: derivatives of reactive oxygen metabolites; hs-cTnT: high sensitivity cardiac troponin T; β: standardized regression coefficient; R²: coefficient of determination.

Figure 3. Receiver-operating characteristic curve analysis for the detection of high CHADS2 scores or elevated hs-cTnT levels based on skin autofluorescence. The maximum Youden’s index indicated that skin autofluorescence values > 2.6 AU and > 2.7 AU are the optimal cutoff points to identify high CHADS2 scores (≥ 2) or elevated hs-cTnT levels (> 0.014 ng/mL), respectively. (a) CHADS2 score. (b) hs-cTnT levels. AF: autofluorescence; AU: arbitrary unit; hs-cTnT: high-sensitivity cardiac troponin T; AUC: area under the curve.
Acknowledgments

The author is grateful to the individuals who participated in this study.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

All patients provided informed consent.

Author Contributions

The author was involved in preparing the study design as well as in the acquisition, analysis, and interpretation of data.

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