Effects of angiotensin II receptor blockers on serum levels of epoxyeicosatrienoic acids and dihydroxyeicosatrienoic acids in patients admitted to a cardiovascular center

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Abstract

Purpose Several clinical studies have demonstrated that angiotensin-converting enzyme inhibitors, but not angiotensin II receptor blockers (ARBs), reduce the risk of non-fatal myocardial infarction and cardiovascular mortality. We found that ARBs inhibited the activity of various cytochrome enzymes in arachidonic acid metabolism, resulting in decreased in vitro production of epoxyeicosatrienoic acids (EETs), which exhibit vasodilation and anti-inflammatory effects, and their subsequent metabolites, dihydroxyeicosatrienoic acids (DHETs). The present study examined the effects of ARBs on serum levels of EETs and DHETs in patients admitted to a cardiovascular center.

Methods A total of 223 patients were enrolled, of which 107 were exposed to ARBs in this study. ARB-free individuals were defined as the control group (n = 116). Serum levels of EETs and DHETs were measured by liquid chromatography–tandem mass spectrometry. Multiple linear regression analyses were carried out to identify covariates for total serum levels of EETs and DHETs.

Results A significant negative association was observed between ARB use and serum EET and DHET levels (p = 0.034), whereas a significant positive association was observed between the estimated glomerular filtration rate (eGFR) and serum EET and DHET levels (p = 0.007). The median serum total EET and DHET level in the ARB group tended to become lower than that in the control group, although the difference was not significant.

Conclusion ARB use and eGFR were significantly associated with total serum levels of EETs and DHETs. Our results suggest that ARBs could affect the concentration of EETs in vivo.

Keywords Angiotensin II receptor blockers · Epoxyeicosatrienoic acids · Dihydroxyeicosatrienoic acids · Serum levels · Multiple linear regression analysis

Introduction

Cytochromes P450 (CYPs), 2C8, 2C9, and 2J2 metabolize arachidonic acid (AA) to four regioisomeric epoxyeicosatrienoic acids (EETs), 14,15-, 11,12-, 8,9-, and 5,6-EET [1]. EETs act as autocrine and paracrine mediators [2] and exert vasodilatory [3] and anti-inflammatory activities [4]. EETs are subsequently metabolized by soluble epoxide hydrolase (sEH) [1] to the corresponding dihydroxyeicosatrienoic acids (DHETs), which are generally less biologically active compared to EETs [2], although Oltmann et al. [5] and Lu et al. [6] reported that DHETs exhibit more potent vasodilatory effects than EETs.

Several studies have reported that the activity of CYP2C8 and CYP2J2 and their polymorphic features constitute a group of enzymes with diminished enzyme activity that is involved
in the development of cardiovascular diseases [7–10]. Oni-
Orisan et al. [11] recently showed that patients with obstruc-
tive coronary artery disease (CAD) have lower levels of plas-
ma EETs and total EETs and DHETs than patients without
apparent CAD. Low levels of circulating total EETs and
DHETs may theoretically increase the risk of cardiovascular
events.

Angiotensin II receptor blockers (ARBs) are the recom-
manded initial treatment for hypertension according to the
2017 ACC/AHA [12] and 2018 ESC/ESH [13] guidelines.
Several clinical trials have suggested that ARBs and angi-
tensin-converting enzyme inhibitors (ACEIs) have a
prophylactic effect against cardiovascular events [14–20].
However, several recent large-scale meta-analyses reported
that ARBs have limited efficacy in preventing cardiovascu-
lar events [21–23]. Hoang et al. [21] reported that ACEIs (but not
ARBs) reduce the risks of non-fatal myocardial infarction
(MI) and cardiovascular mortality in CAD patients. Similar
results have been reported in patients with heart failure [22]
and diabetes mellitus [23].

We previously demonstrated that ARBs inhibit AA metab-
olism via CYP enzymes in vitro, with differing degrees of
inhibition among ARBs [24, 25]. Telmisartan exhibited the
most potent inhibitory effect on AA metabolism among the
seven ARBs investigated, whereas candesartan exhibited little
inhibitory effect [25]. Similar results have been reported by
other researchers [26, 27]; however, it remains unclear wheth-
er ARBs reduce the production of EETs from AA in vivo.

Given this background, we investigated the effects of
ARBs on serum levels of EETs and DHETs in patients admit-
ted to a cardiovascular center. We also explored the covariates
related to total EET and DHET serum levels using multiple
linear regression analysis.

Materials and methods

Study design

A total of 223 patients admitted to the Cardiovascular Center
at Teine Keijinkai Hospital between October 2013 and
October 2017 were enrolled in the study. Individuals contin-
uously exposed to an ARB (azilsartan, candesartan, losartan,
irbesartan, olmesartan, telmisartan, or valsartan) for at least 4
weeks were assigned to the ARB group (n = 107). Individuals
who had not taken any ARB were assigned to the control
group (n = 116). Informed consent was obtained from each
participant included in the study. The study protocol was ap-
proved by the Ethics Committee of Teine Keijinkai Hospital.
All procedures of this study were in accordance with the ethi-
cal standards of the institutional research committee (Ethics
Committee of Teine Keijinkai Hospital, 2013-043) and the
1964 Helsinki declaration and its later amendments or com-
parable ethical standards.

Serum concentrations of EETs and DHETs were deter-
mined using residual serum collected for biochemical exami-
nations. Serum samples containing 0.2 mg/mL of butylated
hydroxytoluene in 50% methanol (final concentration: 3.9 μg/
ml) as an antioxidant were frozen at −30 °C at Teine
Keijinkai Hospital and then transported to Hokkaido
University of Science, where they were stored at −80 °C until
analysis. Concentrations of EETs and DHETs in serum were
measured within 1 week of collection.

Chemicals

Eight eicosanoids (14,15-, 11,12-, 8,9-, and 5,6-EET, and
14,15-, 11,12-, 8,9-, and 5,6-DHET) and their corresponding
deuterated eicosanoids (14,15-, 11,12-, 8,9-, and 5,6-EET-d11,
and 14,15-, 11,12-, and 8,9-DHET-d11) as internal standards
were purchased from Cayman Chemical (Ann Arbor, MI),
except for 5,6-DHET-d11, which was commercially unavail-
able. Therefore, 8,9-DHET-d11 was used as an internal stan-
dard for the determination of 5,6-DHET. OASIS® HLB solid-
phase extraction cartridges (3 cc) were purchased from Waters
(Milford, MA). All other chemicals and solvents were HPLC
or special grade.

Sample preparation

An aliquot of 250 μL of serum was mixed with 50 μL of
internal standard solution and 950 μL of ethanol and placed
on ice for 20 min. The mixture was then centrifuged at 6490×g
for 5 min. The resulting supernatant was loaded onto a
preconditioned OASIS® HLB cartridge, and EETs and
DHETs were extracted using ethyl acetate. The eluate was
evaporated to dryness and reconstituted with 55 μL of 50%
acetonitrile. After centrifugation at 6490×g for 5 min, an ali-
quout of 40 μL of the supernatant was used for liquid
chromatography–tandem mass spectrometry (LC-MS/MS).
Samples were analyzed in duplicate for each subject.

LC-MS/MS conditions

Serum concentrations of EETs and DHETs were determined
using an LC-MS/MS method described previously [24, 28].
The LC-MS/MS system consisted of an Agilent 1200 series
HPLC (Agilent Technologies, Santa Clara, CA) coupled to a
QTRAP® API3200 mass spectrometer (AB Sciei, Framingham,
MA). Separation of EETs and DHETs was conducted at 50 °C using an Ascentis Express C18 column
(2.7-μm particle size, 10 cm × 2.1 mm; Sigma-Aldrich, St.
Louis, MO). Mobile phases A and B consisted of 0.1% formic
acid in acetonitrile and water, respectively. The flow rate was
set at 0.3 mL/min. The gradient program was as follows: 50%
B for 27 min, 50–90% B from 27 to 28 min, 90% B from 28 to 35 min, 90–50% B from 35 to 36 min, and re-equilibration at 50% B from 36 to 43 min. Electrospray ionization was employed to determine EETs and DHETs by multiple reaction monitoring in negative ion mode. Lower limit of quantification (LLOQ) values for each EET and DHET concentration with a signal/noise ratio > 10 were as follows; 0.35 nM (0.11 ng/mL), 0.11 (0.036), 3.6 (1.2), 0.20 (0.064), 0.13 (0.043), 0.13 (0.043), 0.10 (0.034), and 0.077 (0.026) for 14,15-, 11,12-, 8,9-, and 5,6-EET and 14,15-, 11,12-, 8,9-, and 5,6-DHET, respectively.

**Data analysis**

Patient characteristics were compared using chi-squared or unpaired t tests, whereas the Mann-Whitney test was used to analyze differences in levels of EET and DHET regioisomers as well as total levels of EETs and DHETs between the ARB and control groups. Multiple linear regression analyses adjusting for age, sex, body mass index (BMI), smoking status, estimated glomerular filtration rate (eGFR), history of MI, and medications (including ARBs, calcium channel blockers [CCBs], ß-blockers, diuretics, HMG-CoA reductase inhibitors [statins], antiplatelets, anticoagulants, and antidiabetics) were performed using SPSS software (ver. 24.0, IBM Japan, Tokyo, Japan). Patient characteristics and serum levels of EETs and DHETs are expressed as the mean ± SD and median, respectively.

**Results**

**Patient characteristics**

Patient characteristics are shown in Table 1. There were no significant differences between groups with respect to age, sex, systolic blood pressure, smoking status, eGFR, alanine aminotransferase, or history of MI. BMI was significantly lower in the control group than in the ARB group. Diastolic blood pressure (DBP) and aspartate aminotransferase (AST) were significantly higher in the control group compared to the ARB group. CCBs, diuretics, and antiplatelets were prescribed less frequently to the control group.

**EET and DHET serum levels**

Table 2 summarizes EET and DHET serum levels for each group. A large number of the EET serum levels were below the LLOQ; in particular, 8,9-EET could not be detected in any sample in either group. Serum levels of 14,15-EET and 8,9-DHET in the ARB group were significantly lower than those in the control group. The EET/DHET ratio, an indicator of sEH activity, exhibited large interpatient variability.

**Multiple linear regression analysis**

Prior to multiple linear regression analysis, single linear regression analysis was applied to broadly estimate covariates and confirmed that ARB and antiplatelets use, age, and eGFR significantly affected total EET and DHET serum levels (Supplementary Table S1). ARB use and eGFR were considered as covariates for calculating total EET and DHET serum levels in the multiple linear regression analysis (Table 3). A significant negative association was observed between ARB use and total EET and DHET serum levels (p = 0.034), whereas a significant positive association was observed between eGFR and serum levels (p = 0.007).

**Total EET and DHET serum levels**

Figure 1 summarizes the median values for total EET and DHET serum levels for each group. The median total EET and DHET serum level in the ARB group (1.47 nM) tended to become lower than that in the control group (1.83 nM), although the difference was not significant. The adjusted R² (coefficient of determination) value for the multiple regression analysis indicated that eGFR and ARB use contributed only 5.5% to the change in total EET and DHET serum levels (Table 3).

**Discussion**

Serum levels of DHETs, the active metabolites of EETs, decline with decreasing EET levels and affect homeostasis of the cardiovascular system [2, 5, 6]. Clinical studies should therefore assess the effects of medications on serum EET and DHET concentrations. A large number of EET serum levels were below the LLOQ (Table 2), whereas total EET serum levels were higher than total DHET levels. These results were consistent with a previous report [29]. The 14,15-EET concentrations were significantly reduced in patients taking ARBs, but over 90% of samples were below the LLOQ. 8,9-DHTE levels were significantly reduced in patients taking ARBs, but the difference in the median values was small. There were no significant differences in the levels of other eicosanoids or the EET/DHET ratio in patients taking ARBs. The EET/DHET ratio, which indicates sEH activity, was calculated to be 0.310 (36/116) and 0.206 (22/107) in the control and ARB groups, respectively, with large interpatient variability. As the sum of EET and DHET levels is thought to represent EET biosynthesis, the effect of ARBs on reducing EET production from AA via the CYP pathway could be described by the total EET and DHET serum levels.

The other clinical conditions of patients who participated in this study varied, with the exception of taking ARBs. This study examined changes in serum eicosanoid levels due to
ARB use with ethical considerations but did not conduct any interventions in routine medications. It would be useful to investigate the effects of ARBs on the biokinetics of eicosanoids in clinical trials that further classify patient groups.

As shown in Table 1, BMI was significantly lower in the control group than in the ARB group, whereas DBP and AST were significantly higher in the control group than in the ARB group. The differences in BMI and DBP between the two groups were <10%, and the mean AST level in both groups was within the normal range (7–38 IU/L). Therefore, these differences, although significant, would have little influence on the results of this study. CCBs, diuretics, and antiplatelets were co-prescribed more frequently to patients in the ARB group. All patients enrolled in this study were admitted to Cardiovascular Center at Teine Keijinkai Hospital, but the patients in the control group were not always treated for hypertension. The glucuronate conjugate of clopidogrel, a commonly prescribed antiplatelet, exhibits a time-dependent inhibitory effect on CYP2C8 [30, 31]. Clopidogrel was prescribed to 32.8% (38/116) of patients in the control group and 40.1% (43/107) of patients in the ARB group (p = 0.249, chi-squared test). Other than clopidogrel, there was no concomitant use of CCBs, diuretics, and antiplatelets that could affect the metabolism of EETs. Therefore, concomitant drug use would also have a negligible effect on the results of this study.

ARB use was the covariate for calculating the serum levels of total EETs and DHETs (Table 3). The median total EET and DHET serum level in the ARB group tended to become lower than that in the control group, although the difference was not significant (Fig. 1). These results are consistent with studies demonstrating an inhibitory effect of ARBs on AA metabolism in vitro [24, 25].

Renal function was also associated with total EET and DHET serum levels (Table 3). A significant negative correlation was observed between eGFR and age (Spearman’s rank correlation coefficient ρ = −0.552, p < 0.001). Kawabata et al. [32] reported decreased blood concentrations of AA metabolites in geriatric patients. Although the concentrations of EETs and DHETs in urine were not assessed in this study, the positive relationship between eGFR and serum levels of EETs and DHETs could reflect an age-associated decrease in production rather than delayed excretion due to decreased renal function.

The enzymatic activities of CYPs and sEHs are regulated by female hormones/estrogens, resulting in a gender disparity in terms of EET-mediated effects [33]. Experimental human models and pathophysiological studies suggest that enzymes involved in EET biosynthesis and metabolism play a role in controlling blood pressure in a gender-specific manner. Female hormones would protect women from cardiovascular events until menopause, but the risk increases rapidly after

| Table 1 Patient characteristics | Control (n = 116) | ARB (n = 107) | p value |
|----------------------------------|------------------|---------------|--------|
| Age (years)                      | 69.4 ± 11.2      | 72.1 ± 9.8    | 0.067a |
| Sex (male/female)                | 81/35            | 63/44         | 0.088b |
| BMI (kg/m²)                      | 23.4 ± 4.0       | 25.2 ± 3.8    | 0.001a |
| SBP (mmHg)                       | 124.2 ± 18.4     | 127.3 ± 17.8  | 0.244a |
| DBP (mmHg)                       | 72.5 ± 11.4      | 67.4 ± 13.3   | 0.002a |
| Smoking status (current-/ex-/non-smoker) | 20/31/55        | 13/32/46      | –      |
| eGFR (mL/min)                    | 64.2 ± 23.8      | 59.4 ± 24.3   | 0.135a |
| AST (IU/L)                       | 28.4 ± 11.2      | 25.5 ± 9.0    | 0.036a |
| ALT (IU/L)                       | 24.0 ± 13.3      | 21.9 ± 12.6   | 0.227a |
| History of MI                    | 17               | 23            | 0.183b |
| Medication (%)                   |                  |               |        |
| CCBs                             | 36 (31)          | 71 (66)       | < 0.001b |
| β-Blockers                       | 50 (43)          | 47 (44)       | 0.902b |
| Diuretics                        | 18 (16)          | 36 (34)       | 0.002b |
| Statins                          | 58 (50)          | 66 (62)       | 0.079b |
| Antiplatelets                    | 66 (57)          | 75 (70)       | 0.041b |
| Anticoagulants                   | 31 (27)          | 31 (29)       | 0.708b |
| Antidiabetics                    | 23 (20)          | 30 (28)       | 0.150b |

Mean ± SD, a unpaired t-test, b chi-squared test
ARBs angiotensin II receptor blockers, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, eGFR estimated glomerular filtration rate, AST aspartate aminotransferase, ALT alanine aminotransferase, MI myocardial infarction, CCBs calcium channel blockers; Statins: HMG-CoA reductase inhibitors
Multiple linear regression analyses in this study were conducted to calculate total EET and DHET serum levels regardless of gender. Seventy-four of 79 female participants in this study were aged over 60 years and considered menopausal, and they were thought to have as low female hormone levels as low as males, which is why gender was not included in the final model.

Minuz et al. [29] reported lower levels of plasma EETs and total EETs and DHETs in patients with renovascular disease compared with essential hypertensive patients or healthy normotensive subjects. We did not find any significant difference regarding patients with hypertension ($p = 0.518$, Fig. 2), indicating that hypertension has a negligible effect on serum levels of total EETs and DHETs in this population.

Oni-Orisan et al. [11] reported a median plasma level of total EETs and DHETs in patients with obstructive CAD of 2.59 ng/mL, whereas the median serum levels of total EETs and DHETs in this study were 0.497 and 0.620 ng/mL, respectively. The mean ($\pm$ SD) age of patients in the ARB group (72.1 $\pm$ 9.8 years) in our study was higher than that reported by Oni-Oresan et al. (63.6 $\pm$ 10.2) [11]. As the AA concentration in blood decreases with age in humans [32], the discrepancy in circulating levels of EETs and DHETs between the two studies could be explained in part by the difference in mean age of the study populations.

The adjusted $R^2$ value from the multiple regression analysis indicated that eGFR and ARB use contributed only 5.5% to the difference in the serum levels of total EETs and DHETs.
These results suggest that as yet unknown additional factors affect the serum level of total EETs and DHETs. In contrast to ARBs, ACEIs reportedly increase EET levels by inhibiting ACE and increasing bradykinin, which causes vascular relaxation via the release of endothelial relaxing factors, including EETs [35]. This may be related to observations from clinical trials suggesting that ACEIs have a prophylactic effect on cardiovascular events [14–17].

In conclusion, multiple linear regression analysis revealed that ARB use and eGFR are significantly associated with serum levels of EETs and DHETs. The median total EET and DHET serum level in the ARB group tended to become lower than that in the control group, although the difference was not statistically significant. Further studies are thus necessary to elucidate the relationship between serum levels of EETs and DHETs and the risk of cardiovascular events in patients taking ARBs.

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Authors’ contribution All authors contributed to the study conception and design. Data collection and analysis were performed by Yuka Kato, Asuna Senda, Miki Yamashita, Yuki Sasaoka, Minayo Hanada, and Takaki Toda. The research was supervised by Fuminori Hongo, Mitsugu Hirokami, and Takaki Toda. The first draft of the manuscript was written by Yuka Kato and revised by Yuji Mukai, Anders Rane, Nobuo Inotsume, and Takaki Toda. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Not applicable
Compliance with ethical standards

Conflict of interest Takaki Toda has received a research grant from the Japan Society for the Promotion of Science KAKENHI (26460229). The other authors declare that they have no conflicts of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Teine Keijinkai Hospital (no. 2013-043).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable

Code availability Not applicable

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