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Plasma 8-iso-Prostaglandin F2α concentrations and outcomes after acute intracerebral hemorrhage

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ABSTRACT

Background: Higher plasma 8-iso-Prostaglandin F2α concentrations have been associated with poor outcome of severe traumatic brain injury. We further investigated the relationships between plasma 8-iso-Prostaglandin F2α concentrations and clinical outcomes in patients with acute intracerebral hemorrhage.
Methods: Plasma 8-iso-Prostaglandin F2α concentrations of 128 consecutive patients and 128 sex- and gender-matched healthy subjects were measured by enzyme-linked immunosorbent assay. We assessed their relationships with disease severity and clinical outcomes including 1-week mortality, 6-month mortality and unfavorable outcome (modified Rankin Scale score > 2).
Results: Plasma 8-iso-Prostaglandin F2α concentrations were substantially higher in patients than in healthy controls. Plasma 8-iso-Prostaglandin F2α concentrations were positively associated with National Institutes of Health Stroke Scale (NIHSS) scores and hematoma volume using a multivariate linear regression. It emerged as an independent predictor for clinical outcomes of patients using a forward stepwise logistic regression. ROC curves identified the predictive values of plasma 8-iso-Prostaglandin F2α concentrations, and found its predictive value was similar to NIHSS scores and hematoma volumes. However, it just numerically added the predictive values of NIHSS score and hematoma volume.
Conclusions: Increased plasma 8-iso-Prostaglandin F2α concentrations are associated with disease severity and clinical outcome after acute intracerebral hemorrhage.

1. Introduction

Acute intracerebral hemorrhage (ICH) is a common devastating stroke subtype that is associated with high rates of morbidity and mortality despite improvement in neurological intensive care [1,2]. Despite the numerous studies, the pathophysiology of hemorrhagic brain injury remains poorly understood [3,4]. The accumulating evidences show that the oxidative stress plays an important role in this process [5,6]. After ICH, extracellular iron released from heme leads to generation of reactive oxygen species (ROS) [7,8]. The ROS also cause lipid peroxidation, induce large amounts of malondialdehyde, and further impair free-radical scavenging system, causing the oxidative injury and leading to brain edema and neurological deficits [9,10]. Thus, intervention targeted at oxidative stress has been considered to be a potential treatment for patients with ICH [11].

8-Iso-Prostaglandin F2α (8-iso-PGF2α) is derived from phospholipid-bound arachidonic acid by reactive oxygen species-mediated lipid peroxidation and released from membranes by phospholipase A2 activity [12]. Measurement of 8-iso-PGF2α is a reliable tool for the identification of subjects with enhanced rates of lipid peroxidation [13–15]. Enhanced formation of 8-iso-PGF2α has been reported in association with acute coronary syndrome [16], inflammatory bowel disease [17], and acute myocardial infarction [18]. 8-iso-PGF2α is expressed in rat brain neuronal endings after oxidant stimuli [19] and generated in astrocytes following stretch-induced trauma [20] and its plasma concentration is also enhanced during animal spinal cord ischemia [21]. Moreover, 8-iso-PGF2α is increased in the brain interstitial tissue from head trauma patients and identified as a biomarker of oxidative stress after severe human traumatic brain injury [22]. Recently, plasma 8-iso-PGF2α concentration is found to be highly associated with 1-year clinical outcome of severe traumatic brain injury [23]. These results suggest 8-iso-PGF2α may represent a potential biomarker of neurological outcome in ICH. Thus, we sought to determine 8-iso-PGF2α in plasma of patients with acute ICH and evaluate its relation with disease severity and clinical outcome of ICH.

Abbreviations: ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; 8-iso-PGF2α, 8-iso-Prostaglandin F2α.

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2. Materials and methods

2.1. Study population

All patients with acute spontaneous basal ganglia hemorrhage admitted to the Hangzhou First People's Hospital within the first 24 h from stroke during the period of January 2010 to January 2013 were screened for this study. Exclusion criteria were previous stroke, severe head trauma, use of antiplatelet or anticoagulant medication, presence of other prior systemic diseases including uremia, liver cirrhosis, malignancy, and chronic heart or lung disease, undergoing a surgical procedure, refusal of participation, unavailable biomarker measurements or loss of follow-up. Controls consisted of age- and gender-matched healthy volunteers. The study protocol and informed consent approach were approved by the Ethics Committee of the Hangzhou First People's Hospital before implementation. The study individuals or their relatives provided written informed consent to participate in this trial.

2.2. Clinical and radiological assessment

On arrival at the emergency department, a detailed history of vascular risk factors, concomitant medication, National Institutes of Health Stroke Scale (NIHSS) score, body temperature, heart rate, respiratory rate, and blood pressure were taken. Early neurological deterioration was defined as an increase of ≥4 points in the NIHSS score or death at 24 h from symptoms onset [24]. Noncontrast cerebral computed tomography (CT) scans were performed on admission, according to the protocol of the Neuroradiology Department. A follow-up CT was done at 24 h as a clinical routine. The investigators who read them were blinded to clinical information. Hematoma volume was calculated according to the formula $A \times B \times C \times 0.5$, where A and B represent the largest perpendicular diameters through the hyperdense area on CT scan, and C represents the thickness of hematoma [25]. Hematoma growth was defined as hematoma enlargement >33% at 24 h [26].

2.3. Determination of 8-iso-PGF2α in plasma

The informed consents were obtained from study population or family members in all cases before the blood were collected. Venous blood in the healthy individuals or the patients was drawn at study entry or on admission. The blood samples were immediately placed into sterile ethylenediaminetetraacetic acid test tubes coated with ice and centrifuged at 1500 ×*g* for 20 min at 4 °C to collect plasma. Plasma was stored at −70 °C until assayed. The concentration of 8-iso-PGF2α in plasma was analyzed by enzyme-linked immunosorbent assay (ELISA) using commercial kits (Cayman Chemicals) in accordance with the manufactures' instructions. The blood samples were run in duplicate. Researchers running enzyme-linked immunosorbent assay were blinded to all patient details.

Table 1
The characteristics of study population.

Characteristics	Patients
Number	128
Gender (male/female)	78/50
Age (year)	66.2 ± 9.4
Hypertension	109 (85.2%)
Diabetes mellitus	38 (29.7%)
NIHSS score	11.1 ± 4.7
Hematoma volume (ml)	32.3 ± 11.9
Presence of intraventricular hemorrhage	37 (28.9%)
Hemorrhage growth	19 (14.8%)
Early neurological deterioration	23 (18.0%)
Admission time (h)	8.1 ± 5.0
Plasma-sampling time (h)	8.8 ± 4.4
Systolic arterial pressure (mm Hg)	171.4 ± 21.1
Diastolic arterial pressure (mm Hg)	95.6 ± 8.7
Blood glucose level (mmol/l)	11.7 ± 4.2
Plasma C-reactive protein level (mg/l)	11.6 ± 4.4
Plasma 8-iso-Prostaglandin F2α level (ng/ml)	0.54 ± 0.24

The variables are presented as counts (percentage) or mean ± SD as appropriate. NIHSS indicates National Institutes of Health Stroke Scale.

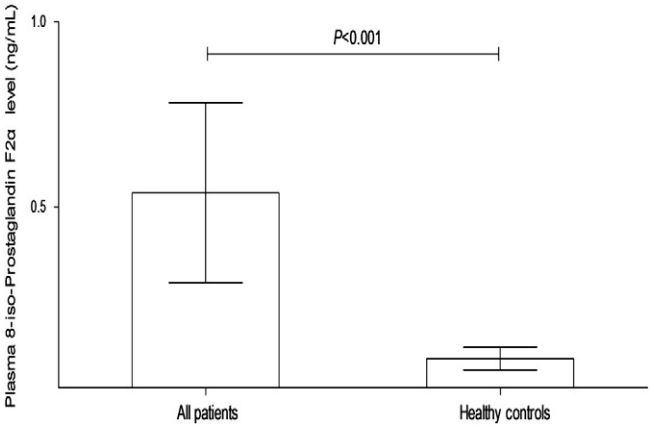

Fig. 1. The change of plasma 8-iso-Prostaglandin F2α concentrations in patients with acute intracerebral hemorrhage. Using *t* test, the admission 8-iso-Prostaglandin F2α concentrations were significantly elevated in all patients compared with healthy control individuals. Data are expressed as mean ± SD.

2.4. End point

Participants were followed up until death or completion of 6 months after stroke. The end points were death after 1 week and unfavorable outcome and death after 6 months. The functional outcome was defined by modified Rankin Scale (mRS) score [27]. 0—no symptoms at all; 1—no significant disability despite symptoms: able to carry out all usual duties and activities; 2—slight disability: unable to carry out all previous activities but able to look after own affairs without assistance; 3—moderate disability: requiring some help, but able to wake without assistance; 4—moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance; 5—severe disability: bedridden, incontinent, and requiring constant nursing care and attention; 6—death. The unfavorable outcome was defined as a mRS score >2 [28]. For follow-up, we used structure telephone interviews performed by 1 doctor, blinded to clinical information.

2.5. Statistical analysis

Statistical analysis was performed with SPSS 19.0 and MedCalc 9.6.4.0. Categorical variables were shown as numbers and percentages. Continuous variables were presented as mean ± standard deviation. Comparisons were made by using chi-square test or Fisher exact test for categorical data as well as unpaired or paired Student's *t* test for continuous variables. Correlations of 8-iso-PGF2α with other variables were assessed by Spearman's correlation coefficient or Pearson's correlation coefficient and followed by a multivariate linear regression. The effect of plasma 8-iso-PGF2α concentrations on the clinical outcome was assessed with the use of multivariate logistic regression analyses. Initially, baseline variables were evaluated for univariate association with clinical outcome. Variables that were significant in univariate analyses were included in a multivariate logistic regression model to determine the risk-adjusted predictors of clinical outcome with odds ratio (OR) and 95% confidence interval (CI). Cut-off point of 8-iso-PGF2α was determined to predict clinical outcome using receiver operating characteristic (ROC) curves. The area under