

Relationship between Digit Ratio and Idiopathic Pulmonary Arterial Hypertension in Japanese Women

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Rec date: Jan 20, 2015; Acc date: Jan 30, 2015; Pub date: Feb 1, 2015

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Abstract

Aim: Endothelin-1 (ET-1) is the key vasoactive mediator in patients with pulmonary arterial hypertension (PAH), and sex steroids are known to influence ET-1 levels. Additionally, the second to fourth digit (2D:4D) ratio is a biometric marker influenced by testosterone concentrations and androgen receptor sensitivity in the uterus, and some reports have linked (2D:4D) ratio to disease predisposition among patients with gender-dependent conditions. Since idiopathic PAH (IPAH) is more prevalent in women, we hypothesized that the 2D:4D ratio could predict a female's predisposition to developing PAH, reflecting an interaction between ET-1 and sex hormones.

Method: This study analyzed 13 female patients with IPAH at Keio University Hospital and 41 unrelated age-matched controls. The right hand of patients and controls was photographed using a digital camera and two experienced scorers measured finger lengths and 2D:4D ratios.

Key findings: The IPAH and control groups had a mean age of 43.2 ± 3.5 and 40.9 ± 1.7 years, respectively. The 2D:4D digit ratio was significantly higher for patients with IPAH than for the control women; 0.975 ± 0.041 vs. 0.940 ± 0.038 , $P < 0.05$. The age at onset of PAH did not correlate with the ratio.

Significance: Female patients with IPAH in this study had a higher 2D:4D digit ratio than age-matched healthy controls, suggesting lower prenatal circulating testosterone levels. In conclusion, the 2D:4D digit ratio is a useful biomarker for IPAH, and prenatal testosterone level could be an important factor for the protection against developing IPAH.

Keywords: Idiopathic pulmonary arterial hypertension; Digit ratio; Development; Estrogen; Testosterone; Estrogen paradox; Endothelin

Introduction

Various digit ratios, and in particular the second to fourth digit ratio (second digit; 2D, fourth digit; 4D), are sexually dimorphic characteristics in humans [1], and indeed, evidence accumulated over the past decade indicates that the 2D:4D ratio is determined by prenatal estrogen and testosterone concentrations [2].

Some studies have already investigated the links between 2D:4D ratio and the etiology of sex-dependent behaviours with respect to immune system disorders, cardiovascular diseases like myocardial infarction [3], some cancers [4], and a number of adult-onset diseases prevalent among men such as amyotrophic lateral sclerosis (ALS) [5]. Therefore, the 2D:4D ratio is a potential predictor of not only fertility, but also sex-dependent disease.

While there are numerous reports of the relationship between 2D:4D ratios and sex predispositions of various diseases, no such study has included patients with idiopathic pulmonary arterial hypertension (IPAH), which has also sex predispositions [6]. In addition, endothelin-1 (ET-1) is the key vasoactive mediator and therapeutic

target in patients with PAH, and an association has been suggested between sex hormones and endothelin [7].

This study thus sought to investigate whether digit ratios have clinical importance as a marker of sexual predisposition to PAH. Since patients with PAH are predominantly women, we hypothesized a link between 2D:4D ratio and disease predisposition in IPAH, reflecting the association between sex steroids and ET-1.

Materials and Methods

Clinical methods

This was a case-control study involving 13 consecutive female patients with IPAH cared for at Keio University Hospital (Tokyo, Japan) from April 2011 to September 2011. We also invited 41 unrelated age-matched healthy women to participate in the study as controls. The diagnosis of PAH was confirmed for each patient by right heart catheterization using diagnostic criteria based on the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines [8].

Finger length measurements

The fingers of patients and controls were designated as 2D and 4D. Photographs of the right hand were taken with the hand supinated and the fingers flattened to full extension on a sheet of white paper with a digital camera placed over the center of the white sheet. Digit length was measured from the basal crease of the digit to the tip using the measurement tool in Adobe Photoshop®. People with faint creases and those with contractures would not be reliably measurable in this study. Rather than selecting patients for these features before entry, which might be biased and arbitrary, we invited consecutive patients to participate and then used an objective rule to exclude hands with poor measurability. Two independent and experienced scorers who were blinded to the case-control status took the measurements from all images.

Statistical methods

Analyses were performed using the statistical package SPSS 19.0. Digit ratios were calculated and their mean values were compared with a t-test because the distribution of the values was normal (Shapiro-Wilk test of normality, $P < 0.05$).

Results

A total of 13 PAH women and 41 control women were studied. Mean ages were not significantly different between the groups at 43.2 ± 3.5 years for the IPAH group and 40.9 ± 1.7 years for controls ($P < 0.05$). The IPAH patient group had significantly higher 2D:4D ratios compared to the healthy control group (mean ratio was 0.975 ± 0.041 and 0.940 ± 0.038 , respectively; $P < 0.05$, Figure 1).

Discussion

The present study revealed that female patients with IPAH had a higher 2D:4D ratio than control women, suggesting that low serum testosterone prenatal levels and high estrogen prenatal levels in the uterus could predispose females to developing PAH.

In general, males have longer fourth digits relative to their second digits than females, and consequently have lower 2D:4D ratios. Developmental and prenatal concentrations of testosterone are linked genetically through the action of homeodomain-containing or homeobox (Hox) genes [9], and differences in androgen exposure in utero with high concentrations of fetal testosterone lead to low 2D:4D ratios. Different digits also show differential distributions of androgen and estrogen receptors [2], which showed that 2D:4D ratio is determined by the balance of prenatal testosterone to estrogen signaling during fetal digit development. Therefore, low 2D:4D ratios may suggest that the result of this paper suggested the onset of IPAH is influenced with the prenatal high testosterone and low estrogen. And as described above, there are some studies which investigated the links between 2D:4D ratio and the etiology of sex-dependent behaviors, therefore, the 2D:4D ratio is a potential predictor of also sex-dependent disease.

IPAH is a rare but devastating disease and, if untreated, leads to right heart failure and premature death. To date, sex remains the most powerful modifier of disease development, as demonstrated by the high prevalence of IPAH in females between the age of 35 and 50 years. Some clinical studies of PAH indicated that abnormalities in estrogen metabolism may play a pathogenic role of PAH [10]. In contrast to these clinical studies, most animal studies have shown that

female sex and estrogen supplementation can have a protective effect against PAH. This apparent contradiction between clinical studies and animal data gave rise to the “estrogen paradox” in PAH [11].

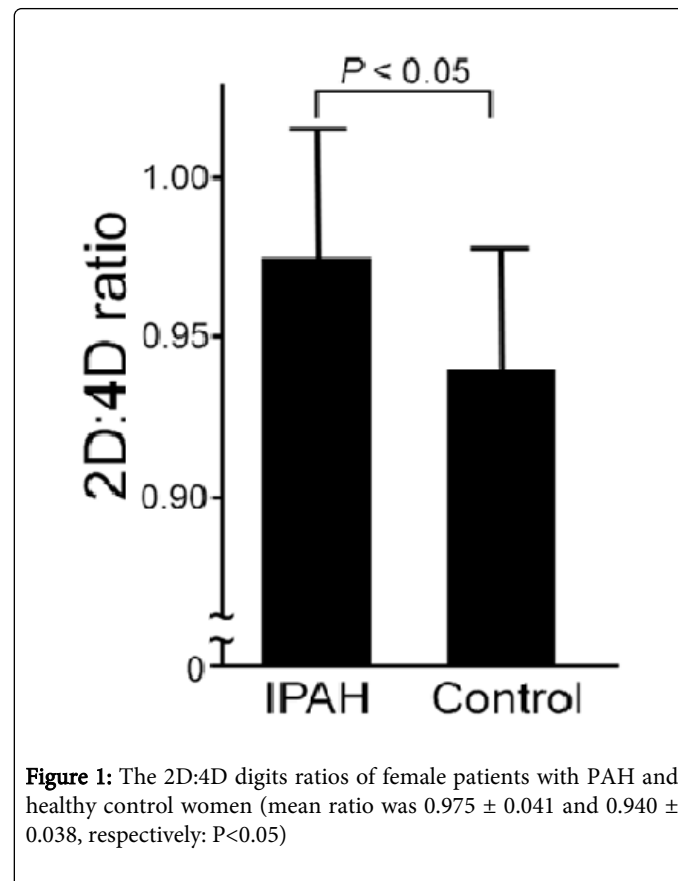


Figure 1: The 2D:4D digits ratios of female patients with PAH and healthy control women (mean ratio was 0.975 ± 0.041 and 0.940 ± 0.038 , respectively; $P < 0.05$)

In addition, there seems to be a clear relationship between sex hormones and the vasoactive mediator endothelin, which is also important in the pathology of PAH. One study showed that estrogen attenuates hypoxia-induced pulmonary ET-1 gene expression in the lung tissue of adult female rats [12], while another found plasma basal levels of ET-1 increased in human males with low testosterone levels [7].

In this context, our study suggested a prenatal sex-steroid predisposition for PAH using the 2D:4D ratio as a marker. This study was limited by being observational only within a single center without notable findings of IPAH patients during prenatal period. However, in the context of the proposed balance between prenatal sex steroids and adult diseases, Chinnathambi et al. [13] also showed that high prenatal testosterone exposure leads to gonad-dependent hypertension during adult life. Little is known about the direct molecular relationship between prenatal sex steroid levels and the development of PAH, and thus our findings raise the novel possibility that testosterone and estrogen in utero could provide insight into the “estrogen paradox” of PAH.

Conclusion

Female patients with IPAH showed a higher 2D:4D digit ratio than healthy subjects, suggesting lower prenatal circulating testosterone levels. In conclusion, the 2D:4D digit ratio is a potentially useful biomarker for IPAH, and prenatal testosterone levels could be the next

research interest which may contribute to protect against developing IPAH.

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