Giant Fold Gastritis Induced by Epoprostenol Infusion in Patients With Pulmonary Arterial Hypertension

Yohei Miura, MD; Masaharu Kataoka, MD; Tomohiro Chiba, MD;
Takumi Inami, MD; Hideaki Yoshino, MD; Toru Satoh, MD

Background: Epoprostenol infusion is the strongest and most convincing therapeutic strategy for severe pulmonary arterial hypertension (PAH). This study investigated the gastrointestinal side effects of epoprostenol.

Methods and Results: The study group of 12 patients treated with epoprostenol (epoprostenol group) and 4 patients without epoprostenol (control group) underwent stomach barium examination, which revealed that the prevalence of giant fold gastritis was significantly higher in the patients treated with epoprostenol (75% in epoprostenol group vs. 0% in control group; $P=0.019$).

Conclusions: Giant fold gastritis may be an important side effect of epoprostenol infusion.

Key Words: Epoprostenol; Giant fold gastritis; Pulmonary arterial hypertension; Stomach barium examination

Epoprostenol infusion is the strongest and most convincing therapeutic strategy for severe pulmonary arterial hypertension (PAH),¹ but has some potential side effects such as thrombocytopenia and disturbed thyroid function.² We found giant fold gastritis as a pathological finding in some deceased patients with idiopathic or heritable PAH who had been treated with epoprostenol. Therefore, we conducted a clinical study to investigate the prevalence of giant fold gastritis in idiopathic or heritable PAH patients treated with epoprostenol.

We enrolled 12 PAH patients treated with epoprostenol

(epoprostenol group) and 4 untreated PAH patients (control group). Inclusion criteria were female patients aged 20–60 years with idiopathic or heritable PAH who agreed to participate in this study, and exclusion criteria were those who disagreed. All enrolled patients gave informed consent, and the hospitals' institutional review board approved the study protocol and the analysis of data. All patients underwent stomach barium examination. At the timing of this examination, although the median [interquartile range (IQR)] albumin level was significantly lower in the epoprostenol group (4.0 [IQR 3.7–4.4] g/dL in

Figure. Representative images of stomach barium examination in patients with pulmonary arterial hypertension (PAH). (A) Giant fold gastritis in a PAH patient treated by epoprostenol. (B) Control image without giant fold gastritis in a PAH patient not treated with epoprostenol.

Received April 2, 2018; revised manuscript received July 12, 2018; accepted August 7, 2018; released online August 22, 2018
Time for primary review: 84 days

Division of Cardiology, Second Department of Internal Medicine (Y.M., T.I., H.Y., T.S.), Department of Pathology (T.C.), Kyorin University School of Medicine, Tokyo; Department of Cardiology, Keio University School of Medicine, Tokyo (M.K.), Japan
Mailing address: Masaharu Kataoka, MD, Department of Cardiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. E-mail: m.kataoka09@keio.jp

ISSN-1346-9843 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

Table. Giant Fold Gastritis Detected by Stomach Barium Examination

Group / Age (years)	Sex	BMI (kg/m ²)	Duration of epoprostenol use (years)	Dose of epoprostenol (ng/kg/min)	Giant fold gastritis	Digestive symptoms	PAH-specific drugs (dose/day)	Stomach medicines (dose/day)
Epoprostenol group								
33	F	19	3	38	+	–	Macitentan 10 mg+ Tadalafil 40 mg	–
35	F	24	5	34	+	–	Macitentan 10 mg	–
38	F	26	9	52	+	Heart burn	Bosentan 250 mg+ Tadalafil 40 mg	–
47	F	16	11	55	+	Diarrhea	Bosentan 250 mg+ Sildenafil 60 mg	–
47	F	18	9	26	+	–	Bosentan 250 mg+ Sildenafil 60 mg	–
48	F	22	5	113	+	Diarrhea	Macitentan 10 mg+ Riociguat 7.5 mg	Famotidine 20 mg
51	F	21	7	31	+	–	Bosentan 250 mg+ Tadalafil 40 mg	–
51	F	21	10	46	+	Diarrhea	Ambrisentan 5 mg+ Sildenafil 60 mg	–
52	F	19	2	32	+	Diarrhea	Ambrisentan 5 mg+ Tadalafil 40 mg	Esomeprazole 20 mg
37	F	18	2	110	–	Diarrhea	Macitentan 10 mg+ Tadalafil 40 mg	–
43	F	18	12	28	–	–	Ambrisentan 10 mg+ Riociguat 7.5 mg	–
49	F	16	15	55	–	Diarrhea	Macitentan 10 mg+ Sildenafil 60 mg	–
Control group								
29	F	33	No epoprostenol use		–	Melena	Macitentan 10 mg+ Riociguat 7.5 mg	–
31	F	19			–	–	Macitentan 10 mg+ Riociguat 7.5 mg	–
37	F	22			–	–	Macitentan 10 mg+ Sildenafil 60 mg+ Beraprost 360 µg	–
62	F	19			–	–	Macitentan 10 mg+ Riociguat 7.5 mg	–

Giant fold gastritis was diagnosed by radiology specialists when the wall thickening was ≥ 4 mm with dilatation of the stomach after use of a foaming agent. BMI, body mass index; PAH, pulmonary arterial hypertension.

epoprostenol group vs. 4.5 (IQR 4.4–4.6) g/dL in control group, $P=0.045$), hemodynamic and other biomarkers were not significantly different between the 2 groups [mean pulmonary arterial pressure, 27 (IQR 21–32) mmHg vs. 35 (IQR 28–40) mmHg, $P=0.078$; pulmonary vascular resistance, 4.2 (IQR 2.8–5.8) Wood units vs. 6.2 (IQR 4.9–7.0) Wood units, $P=0.078$; cardiac output, 4.7 (IQR 4.0–5.4) L/min vs. 4.5 (IQR 3.5–5.4) L/min, $P=0.314$; B-type natriuretic peptide, 20.8 (IQR 7.7–42.8) pg/mL vs. 27.8 (IQR 6.6–60.4) pg/mL, $P=0.973$; in epoprostenol vs. control group, respectively]. Medication with regard to other PAH-specific drugs and gastric medicines were not significantly different between the 2 groups by Fisher's exact test.

Stomach barium examination revealed that the prevalence of giant fold gastritis was significantly higher in the patients treated with epoprostenol (9 of 12 patients (75%) in the epoprostenol group vs. 0% in control group; $P=0.019$; odds ratio=24.43, 95% confidence interval, 1.027–581.1] (Table). Figure is a representative image of giant fold gastritis observed in patients treated with epoprostenol. In 7 of the 9 patients with giant fold gastritis, *Helicobacter pylori* infection was negative on serum antibody test; the remaining patients were not tested.

The underlying cause of giant fold gastritis observed in

this study could not be determined because no pathological studies have been conducted so far. And because of the small number of subjects in each group, it is unclear whether giant fold gastritis is associated with epoprostenol or not. It may be caused by other PAH-specific drugs or the patients with PAH happened to have giant fold gastritis before treatment. However, our results suggest that the possibility of epoprostenol causing giant fold gastritis cannot be ruled out: if patients who have been treated with epoprostenol long-term show hemodynamic exacerbations, the possibility of impaired absorption of PAH-specific oral vasodilator drugs caused by giant fold gastritis should be taken into consideration. Collaborative large studies including pathological analysis will be necessary for further research into the relationship between epoprostenol infusion and the occurrence of giant fold gastritis.

References

- Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004; **351**: 1425–1436.
- Ogawa A, Matsubara H, Fujio H, Miyaji K, Nakamura K, Morita H, et al. Risk of alveolar hemorrhage in patients with primary pulmonary hypertension-anticoagulation and epoprostenol therapy. *Circ J* 2005; **69**: 216–220.