High-resolution Manometry and Globus: Comparison of Globus, Gastroesophageal Reflux Disease and Normal Controls Using High-resolution Manometry

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Background/Aims
Globus is a foreign body sense in the throat without dysphagia, odynophagia, esophageal motility disorders, or gastroesophageal reflux. The etiology is unclear. Previous studies suggested that increased upper esophageal sphincter pressure, gastroesophageal reflux and hypertonicity of esophageal body were possible etiologies. This study was to quantify the upper esophageal sphincter (UES) pressure, contractile front velocity (CFV), proximal contractile integral (PCI), distal contractile integral (DCI) and transition zone (TZ) in patient with globus gastroesophageal reflux disease (GERD) without globus, and normal controls to suggest the correlation of specific high-resolution manometry (HRM) findings and globus.

Methods
Fifty-seven globus patients, 24 GERD patients and 7 normal controls were studied with HRM since 2009. We reviewed the reports, and selected 5 swallowing plots suitable for analysis in each report, analyzed each individual plot with ManoView. The 5 parameters from each plot in 57 globus patients were compared with that of 24 GERD patients and 7 normal controls.

Results
There was no significant difference in the UES pressure, CFV, PCI and DCI. TZ (using 30 mmHg isobaric contour) in globus showed significant difference compared with normal controls and GERD patients. The median values of TZ were 4.26 cm
(interquartile range [IQR], 2.30-5.85) in globus patients, 5.91 cm (IQR, 3.97-7.62) in GERD patients and 2.26 cm (IQR, 1.22-2.92) in normal controls ($P = 0.001$).

**Conclusions**

HRM analysis suggested that UES pressure, CFV, PCI and DCI were not associated with globus. Instead increased length of TZ may be correlated with globus. Further study comparing HRM results in globus patients within larger population needs to confirm their correlation.

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**Key Words**

Gastroesophageal reflux; Globus; High-resolution manometry

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**Introduction**

Globus is defined as a sense of lump, a retained food bolus, or tightness in the throat. The symptom is nonpainful, frequently improves with eating, commonly is episodic, and is unassociated with dysphagia or odynophagia. Globus is unexplained by structural lesions, gastroesophageal reflux disease (GERD), or histopathology-based esophageal motility disorders.

Galmiche et al suggested 5 diagnostic criteria for globus as persistent or intermittent, nonpainful sensation of a lump or foreign body in the throat, occurrence of the sensation between meals, absence of dysphagia or odynophagia, absence of evidence for gastroesophageal reflux and absence of histopathology-based esophageal motility disorders.

Globus is not an uncommon symptom. Nearly half of the general population has had intermittent symptoms resembling globus, while more severe and distressing symptoms comprise up to 4% of referrals to otolaryngological specialists.²,³ Some authors suggested that globus is linked with a wide range of psychopathology in men, notably depression and somatization disorder, but there is no clearly accepted etiology nowadays.⁴,⁵ Previous studies suggested that increased upper esophageal sphincter pressure,³,⁶,⁷ gastroesophageal reflux⁸,⁹ or hypertonicity of esophageal body¹⁰ are a possible etiologies of globus.

Recently, high-resolution manometry (HRM) capable of pressure monitoring from the pharynx to the stomach together with pressure topography plotting was used for clinical diagnosis of functional esophageal disorders and clinical researches.¹¹ Based on the recent reports, we decided to collect HRM analysis data in patients with globus symptom, thereafter compared the HRM analysis parameters including upper esophageal sphincter (UES) pressure, contractile front velocity (CFV), proximal contractile integral (PCI), distal contractile integral (DCI) and transition zone (TZ) in patients with globus, gastroesophageal reflux (GERD) patients without globus and normal controls to suggest the correlation specific HRM findings for globus.

**Materials and Methods**

**Subjects**

Total of 83 patients (59 globus patients and 24 GERD patients) who were referred to the Department of Otolaryngology and Gastroenterology at Kangbuk Samsung Hospital between January 2009 and February 2012 were studied with 36 channel HRM. We reviewed their clinical records and the HRM reports retrospectively. Two patients among the globus dropped out because their HRM records had insufficient contents of analyzable parameters. Then, we conducted prospective HRM studies in 7 normal healthy volunteers.

Total 88 patients (57 globus patients, 24 GERD patients and 7 normal controls) were enrolled in our retrospective HRM comparative study.

Fifty-nine patients, who complained isolated globus symptom (as lump or foreign body sense in the throat) without dyspepsia or pyrosis in Gastroenterology or ear, nose and throat (ENT) out-patient department (OPD), were enrolled as globus group retrospectively. Twenty-seven patients via ENT department had laryngoscopic examination in the ENT OPD. All referred by ENT department had no laryngopharyngeal reflux. Twenty-four GERD patients were enrolled via Gastroenterology OPD. They had dyspepsia and/or typical heart burn, and were diagnosed as GERD by esophagogastroduodenoscopy (EGD). But, they did not take esophageal impedance pH monitoring test. We defined
endoscopic GERD by the Los Angeles classification. “Red streak,“ “ulcer“ and “erosion“ on esophagogastric junction were thought as typical findings of GERD. But, the findings of minimal changes, such as mucosal edema, friability or erythema, were not excluded in our definition of endoscopic GERD. Four patients with minimal changes were included in GERD patients group in our study.

Seven normal controls were healthy volunteers for the study. They did not have any symptoms of globus and GERD. They did not undergo EGD, laryngoscopy or esophageal impedance pH monitoring.

The study was approved by the Kangbuk Samsung Hospital Institutional Review Board.

High-resolution Manometry Protocol

HRM study was performed using a 4.2 mm outer diameter solid-state manometric assembly with 36 circumferential sensors spaced at 1 cm intervals (Sierra Scientific Instruments. Los Angeles, CA, USA). Before HRM recording, transducers were calibrated at 0 and 350 mmHg using externally applied pressure. Studies were done in a sitting position after at least 6 hour fast. After transnasal placement of manometry assembly, it was positioned to record from the hypopharynx to the stomach with 3 intragastric sensors. Then, the catheter was fixed to the nose by taping. Our manometric protocol also included a 5 minute period to assess basal sphincter pressure and ten 5 mL water swallows.

High-resolution Manometry Data Analysis

Manometric data were analyzed using software customized for processing binary manometric data into isocontour pressure plots and spatial pressure variation plots, ManoView (Sierra Scientific Instruments) and MATLAB (The MathWorks, Natick, MA, USA).

First, data were corrected for the thermal sensitivity of the pressure-sensing elements using the thermal compensation function of ManoView.

After thermal correction, the 5 minute recording before the first test swallow was subdivided into consecutive 30 second intervals. The position of the UES was readily identified on the pressure topography plots as a high-pressure zone demarcated by an abrupt increase in pressure relative to atmospheric pressure at its proximal margin and intrathoracic pressure at its distal margin. The UES, detectable as a high-pressure zone, was analyzed with a special software model (eSleeve), which allowed to analyze the highest pressure in the UES, irrespective of movement artifacts and the pressures during inspiration and expiration, was determined as Kwiatek et al did.

We also defined the lower margin of the UES and esophagogastric junction (EGJ) from resting state of esophagus to differentiate proximal and distal esophageal contraction from UES and EGJ as Ghosh et al did. The PCI and the DCI were calculated with 30 mmHg isobaric contour pressure levels. CFV was measured as the slope of the best-fit tangent to the 30 mmHg isobaric contour pressure levels automatically by ManoView.

TZ was easily localized between the proximal and distal esophageal contractile segments as the locus of the nadir pressure amplitude during peristalsis. Quantifying a spatial length and temporal duration of the TZ at 30 mmHg isobaric contour pressure levels was calculated by using ManoView (Fig. 1).

The 5 parameters (UES pressure, CFV, PCI, DCI and TZ) were obtained from 5 each swallowing plot, that was suitable for analysis due to relative discrete pressure difference during peristalsis. The parameters in 57 globus patients were compared with that of 24 GERD patients and 7 normal controls.

Statistical Methods

The 5 parameters (UES pressure, CFV, PCI, DCI and TZ) were summarized using medians with 5th-95th percentile range. The Kruskal-Wallis non-parametric test and ANCOVA test were used to compare patients groups and controls. Post hoc analyses were performed with Mann-Whitney U test for subgroup analysis in 3 each group (normal vs. GERD, normal vs.
Table 1. Subjects Demographics

|                       | Normal controls | Patient controls (GERD) | Globus |
|-----------------------|-----------------|-------------------------|--------|
| Numbers               | 7               | 24                      | 57     |
| Age (mean [range], yr)| 43 (20-50)      | 51 (20-75)              | 57 (30-81) |
| Gender (F:M)          | 5:2             | 10:14                   | 41:16  |
| Initial visiting department (GI:ENT) | - | 24:0 | 30:27 |
| EGD (+)               | -               | 24                      | 38     |
| Laryngoscope (+)      | -               | 0                       | 27     |

GERD, gastroesophageal reflux disease; GI, gastrointestinal medicine department; ENT, ear, nose and throat department; EGD, esophagogastroduodenoscopy.

Table 2. Comparison of High-resolution Manometry Parameters in Globus, Gastroesophageal Reflux Disease and Normal Controls

|                         | Normal               | Patient controls (GERD) | Globus               | P-value |
|-------------------------|----------------------|-------------------------|----------------------|---------|
| UES pressure (mmHg)     | 84.50 (57.70-93.60)  | 60.15 (43.42-82.10)     | 59.40 (40.95-80.25)  | 0.171   |
| CFV (cm/sec)            | 3.20 (2.90-4.00)     | 3.35 (2.92-4.47)        | 3.40 (2.90-4.00)     | 0.865   |
| PCI (30 mmHg IBC)       | 112.82 (103.84-307.60) | 130.70 (25.30-211.39)  | 126.00 (49.50-231.30) | 0.923   |
| DCI (30 mmHg IBC)       | 1,030.78 (849.50-1,388.32) | 758.78 (447.73-1,090.36) | 786.00 (447.50-1,335.50) | 0.299   |
| TZ (cm)                 | 2.26 (1.22-2.92)     | 5.91 (3.97-7.62)        | 4.26 (2.30-5.85)     | 0.001   |

GERD, gastroesophageal reflux disease; UES, upper esophageal sphincter; CFV, contractile front velocity; PCI, proximal contractile integral; IBC, isobaric contour; DCI, distal contractile integral; TZ, transition zone.

Data are presented as median (interquartile range).

Results

Subjects Demographics

Subjects demographics are shown in Table 1. Fifty-seven globus patients, 24 GERD patients, and 7 normal controls were enrolled in our study. Their median age were 43 (20-50), 51 (20-75), and 57 (30-81) years, respectively. Female was dominant (72%) in globus patients, but not in GERD patients (42%). Laryngopharyngeal reflux was ruled out in 27 patients via ENT department by laryngoscopic examination in ENT OPD. But, the other 30 globus patients and 24 GERD patients who were enrolled via Gastroenterology OPD did not take laryngoscopy. Total of 62 patients underwent endoscopy (30 in globus and 24 in GERD) (Table 1).

Comparison of High-resolution Manometry Parameters

There was no significant differences in the UES pressure, CFV and body tonicity (PCI and DCI). But, TZ (spatial gap between the termination of the proximal contraction and the initiation of the distal contraction using a 30 mmHg isobaric contour) in globus patients showed significant difference compared with normal controls and patient controls (GERD patients). The median values of TZ were 4.26 cm (interquartile [IQR], 2.30-5.85) in globus, 5.91 cm (IQR, 3.97-7.62) in patient controls, and 2.26 cm (IQR, 1.22-2.92) in normal controls ($P = 0.001$). There was statistically significant difference in median value of TZ in each subgroup comparison ($P$-value was 0.011 in comparison of globus to GERD, 0.013 in comparison of globus to normal, and 0.000 in GERD to normal) (Table 2 and Fig. 2).

![Figure 2](image-url). The distribution box plot of measured value of transition zone in globus, gastroesophageal reflux disease (GERD) and normal controls. Above box plot shows differences of distributions and median values of measured transition zone value among the 3 groups.
Globus sensation (also globus pharyngeus and globus hyster-
icus) is common in the general population. Thompson and
Heaton\textsuperscript{16} reported that 45 percent of 147 healthy volunteers had
experienced globus sensation at least once. It was 3 times more
common in women than in men who were under the age of 50,
while there was no difference in prevalence between men and
women over the age of 50.\textsuperscript{17} Similar gender ratio was observed in
our study population. But, their median age was over the age of
50. The etiology is still unclear, and it has been proposed that va-
rieties of disorders are associated with globus and it’s clinical as-
pects are overlapped somewhat. Some authors suggested that an
association between globus sensation and GERD.\textsuperscript{3,6,19} Chen et
al\textsuperscript{18} suggested an association with visceral hypersensitivity. Other
authors suggested that hypertensive UES pressure was related with
globus.\textsuperscript{3,6,20}

In our study, HRM analysis suggested that UES pressure,
CFV and esophageal tonicity (PCI and DCI) were not associated
with globus sensation. But increased length of TZ may be corre-
lated with globus. TZ is localized stereotypical morphologic fea-
ture of peristalsis between the proximal and distal esophageal seg-
mental contraction. Ghosh et al\textsuperscript{15} reported that 34.6% of the pa-
tients with spatial and/or temporal TZ defects had unexplained
dysphagia, which was significantly more than seen with normal
TZ dimensions (19.8%), and TZ defects greater than 2 cm in
length and 1 second in duration were strongly associated with
otherwise unexplained dysphagia, occurring in 57% of the 25 pa-
tients, and it might be related to dysphagia in a minority of pa-
tients (< 4% in this series).\textsuperscript{15}

We would like to address about some hypothesis based on the
previous study by Ghosh et al.\textsuperscript{21} presented at the planning stage of
our research. Ghosh et al\textsuperscript{21} showed that impaired coordination
of upper and lower contractile wave was associated with bolus re-
tention of TZ, and insufficient strength of TZ, and/or increased
spatial separation between upper and lower contractile wave
(increased TZ) resulted in the failure of bolus fluid clearance
from the TZ. The strength of TZ was reduced as the spatial sepa-
ratio became wider.

Two hypotheses were needed for explaining our results based
on their study. First one was that bolus retention itself or im-
paired clearance of bolus retention might have caused the symp-
tom of globus or GERD. Some studies showed that functional
anatomical location (TZ) at aortic arch level was common site for
symptomatic bolus impaction and esophageal hypersensitivity.\textsuperscript{22}
We thought that first hypothesis might be the possible explana-
tion. Second hypothesis was that someone could have had the
symptom of globus and the other could have had the symptom of
GERD depending on the amount of impaired bolus retention
(who had larger amount of impaired bolus retention could experi-
ence the GERD symptom as pyrosis, and who had smaller
amount could feel globus). It was difficult to accept that assump-
tion and hardly more difficult to clarify the relationship. We hope
that ongoing, well designed prospective study using HRM and
24-hour pH impedance monitoring will reveal that relationship.

As Rakshit and de Caestecker\textsuperscript{4} pointed out, our study also
had same shortcomings. It was retrospective comparative study,
and enrolled subjects were small population, especially the nor-
mal controls. Globus patients in our study were not purely se-
lected by Rome III criteria. Majority of globus patients and some
of GERD patients did not take EGD or pH monitoring to check
gastroesophageal reflux. Furthermore, laryngopharyngeal re-
flux that was also one possible cause of globus was not completely
ruled out in some of the globus patients enrolled via gastro-
intestinal OPD without laryngoscopic evaluation. Kwiatek et al\textsuperscript{6}
suggested that hyperdynamic changes of UES pressure corre-
lated with globus rather than hypertonicity of UES pressure
itself. We have now regrets that we represented the UES pres-
sure by just only maximum pressure of UES.

Despite of recent evaluation with HRM, globus has obscure
etiology. Further prospective controlled study comparing HRM
analysis data in globus group with larger normal controls is need-
ed to confirm their correlation.

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