

# The Role of Gastroesophageal Reflux in Provoking High Blood Pressure Episodes in Patients With Hypertension

Zhi-tong Li, MD,\* Feng Ji, PhD,\* Xin-wei Han, PhD,\* Li Wang, PhD,\*  
Yong-qiang Yue, PhD,† and Zhong-gao Wang, MD\*

**Goals:** We assessed the relationship between gastroesophageal reflux disease (GERD) and hypertension and whether antacid therapy could be used to control blood pressure (BP) on hypertension in patients with GERD.

**Background:** Gastroesophageal reflux disease (GERD) may provoke cardiovascular disease. Many factors are involved in the development of essential hypertension, but whether GERD has a role needs further study.

**Study:** Patients with essential hypertension (n=86) were studied by 24-hour continuous BP monitoring and esophageal impedance and pH monitoring. Patients fulfilling the GERD criteria received 14-day therapy with omeprazole (20 mg twice a day), and the effect on BP was studied.

**Results:** Of the 86 essential hypertension patients, 38 (44.2%) had GERD. Among these 38 patients, 494 episodes of pathologic reflux (PR), and 684 episodes of high BP were recorded. PR was significantly more common at nighttime especially when supine. Of the 684 episodes of hypertension, 102 (14.9%) were synchronous with PR. GERD patients had significantly higher nocturnal BP than non-GERD patients. Antacid therapy brought about significant reduction in all esophageal monitoring parameters as well as in BP parameters in GERD patients.

**Conclusions:** This study demonstrated that there is significant correlation between hypertension and GERD. Antacid therapy can restore normal esophageal pH and help maintain normal BP.

**Key Words:** GERD, hypertension, blood pressure monitoring, esophageal impedance and pH monitoring

(*J Clin Gastroenterol* 2018;52:685–690)

An estimated 1 billion individuals have hypertension worldwide, with 50 million individuals in the United

States alone.<sup>1</sup> Its prevalence is increasing and, by 2025, it is estimated that the number of adults with hypertension will be around 1.56 billion.<sup>2</sup> Obesity or overweight and disorders of lipid and uric acid metabolism are the primary risk factors of essential hypertension. Gastroesophageal reflux disease (GERD), another common medical condition, shares many of the same risk factors with hypertension, such as obesity, male sex, and alcohol drinking. In Western countries, approximately 10% to 20% of adults experience the typical symptoms of GERD—heartburn and/or acid regurgitation—at least once a week.<sup>3</sup> GERD has been linked to a number of extraesophageal symptoms and disorders. The Montreal Definition and Classification of GERD have recognized that cough, laryngitis, asthma, and dental erosion can be manifestations of the GERD syndrome.<sup>4</sup> Lux et al<sup>5</sup> used simultaneous monitoring of esophageal function and electrocardiographic activity to demonstrate that GERD was present in 40% of patients with angiographically proven coronary artery disease (CAD). Studies on the association between GERD and cardiovascular disease have reported conflicting results. Although 1 study demonstrated that GERD was associated with an increased prevalence of hypertension,<sup>6</sup> another study found that coronary heart disease and hypertension were not correlated with GERD, although nonvalvular atrial fibrillation was significantly associated with symptomatic GERD.<sup>7</sup> Interestingly, Sarnelli et al<sup>8</sup> found the prevalence of hypertension to be significantly lower in GERD patients than in non-GERD patients and suggested that GERD might protect against hypertension by inducing changes in the dietary habits of patients.

Many factors are involved in the development of essential hypertension, but whether GERD has an increased risk of hypertension with an increased prevalence of  $\geq 1$  hypertension risk factors. The availability of methods such as 24-hour blood pressure (BP) and esophageal impedance and pH monitoring has made investigation of this relationship possible. The aim of this study was to determine whether there was a relationship between GERD and episodes of high BP in patients with essential hypertension, and to assess whether short-term antacid therapy for GERD could lower BP.

## MATERIALS AND METHODS

### Compliance With Ethical Standards

Informed consent was obtained from each patient included in the study. The studies have been approved by the First Affiliated Hospital of Zhengzhou University ethics committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Received for publication May 14, 2017; accepted August 10, 2017.

From the \*Department of Interventional Radiology and GERD; and †Department of Cardiology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, P.R. China.

Z.-t.L. and F.J.: patient enrollment, GERD diagnosis, experimental design, manuscript writing and revision. X.-w.H.: experimental design and interpretation. L.W. and Y.-q.Y.: patient enrollment, data collection, and statistical analysis. Z.-g.W.: experimental design, analysis, and critical review.

The authors declare that they have nothing to disclose.

Address correspondence to: Zhong-gao Wang, MD, Department of Interventional Radiology and GERD, the First Affiliated Hospital of Zhengzhou University, 1 East Jian She Road, Zhengzhou, Henan Province 450052, P.R. China (e-mail: zhonggaowangfirst@126.com).

Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/MCG.0000000000000933

## Study Population

A total of 86 patients with essential hypertension, seeking care in the Cardiology Clinic and Department of Gastroesophageal Reflux Disease in the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, were recruited consecutively. They included 49 men and 37 women, with a mean age of 53.8 years (age range, 30 to 80 y).

he medical data of all patients with essential hypertension showed mild to moderate hypertension according to the World Health Organization (WHO) criteria at routine examination in adult. According to these criteria, hypertension is defined as systolic BP  $\geq 140$  mm Hg and/or diastolic BP  $\geq 90$  mm Hg, or history of therapy with antihypertensive medication. Patients with secondary hypertension and target organ damage were excluded from the study.

GERD was diagnosed if the typical symptoms of heartburn and regurgitation were accompanied by endoscopic evidence of esophagitis, or abnormal esophageal pH, a DeMeester score  $\geq 14.72$  with symptom correlation of  $\geq 50\%$ , or  $>73$  reflux episodes per day during 24-hour ambulatory impedance monitoring.<sup>9</sup> Any patients who had symptoms suggestive of reflux esophagitis and had received 14-day therapy with proton-pump inhibitors (PPIs) were also assumed to have GERD. Patients with large hernias and obstructive sleep apnea syndrome (OSAS) were excluded from the study, because these conditions could cause changes in BP,<sup>10,11</sup> interfere with the results of the study.

Pathologic reflux (PR), that is, reflux associated with the onset of symptoms (such as heartburn, regurgitation, chestpain and so on), was indicated by a fall in esophageal pH to  $<4$  for  $>5$  minutes.<sup>12</sup>

## Secondary Study End Points

All patients underwent endoscopy, simultaneous 24-hour continuous BP monitoring, esophageal impedance and pH monitoring. Patients on any form of antacid therapy were asked to stop treatment for at least 2 weeks before the study. Antihypertensive therapy was not withheld or altered during the study. Twenty-four hour continuous BP monitoring and impedance-pH monitoring were carried out at the same time.

The 24-hour BP monitoring device consisted of an inflatable cuff attached to a small computer, which weighed about 500 grams. It was worn over the shoulder or on a belt. On the basis of study of Dobrzycki et al<sup>12</sup> and Lam et al,<sup>13</sup> hypertension provoked by GERD was defined as elevation of systolic BP to  $\geq 140$  mm Hg and/or diastolic BP to  $\geq 90$  mm Hg during and for up to 10 minutes after a PR episode. In our methodology, BP monitoring was set to monitor once every 10 minutes over a 24-hour time period. Information on the BP measurements was recorded on tape and could be downloaded to a computer. The following variables were assessed: daytime (awake activity) BP, nocturnal (sleep) BP, diurnal average systolic and diastolic BP, and the percentage fall in nocturnal BP (ie, average daytime BP—average nocturnal BP/average daytime BP). According to the percentage fall in nocturnal BP, patients could be classified as “dippers” (those with 10% to 20% fall in BP at night) and “nondippers” (those with  $<10\%$  fall in BP at night). When the decrease in systolic BP and diastolic BP were discordant, only the systolic BP was considered.

Esophageal impedance-pH was measured with an antimon electrode catheter (Syntetics, Sweden). For each patient, the electrode catheter was placed 5 cm above lower esophageal sphincter. The indicators and standards for

impedance-pH monitoring were adapted from Kim.<sup>14</sup> The following parameters were evaluated: (1) total duration for which pH remained  $<4$ , (2) percentage duration for which pH was  $<4$  in the upright position, (3) percentage duration for which pH was  $<4$  in the recumbent position, and (4) number of times pH decreased to  $<4$ .

## Primary Study End Points

All cases of high BP recorded during a PR episode were considered time-dependent on PR. Patients who had at least 1 episode of high BP in response to PR were identified. The relationship between GERD and hypertension was evaluated by episode of PR and high BP. These patients were then administered a 14-day course of omeprazole (20 mg twice a day). On the 14th day of the therapy, simultaneous continuous esophageal impedance-PH and BP monitoring was repeated at the similar external environment (eg, similar time of sleep, daily activity, etc.).

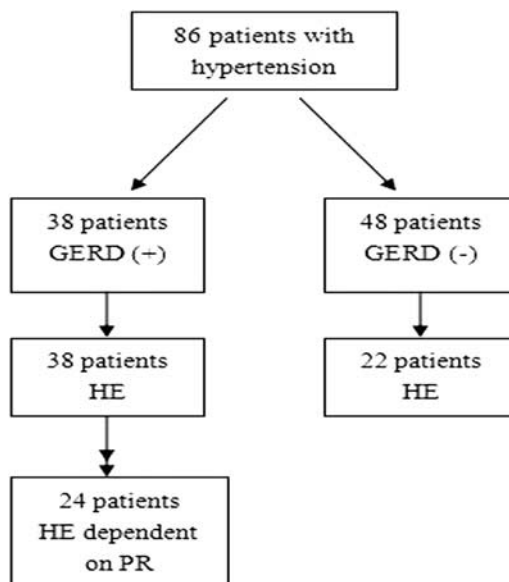
## Data Analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL) and GraphPad InStat version 3.06 (GraphPad Software, San Diego, CA). The data were reported as maximum, minimum, mean, and SD for normally distributed variables. The nonparametric Mann-Whitney *U* test was used when the data were not normally distributed. Regression analysis was used to determine the relationship between hypertension and GERD. Pearson  $\chi^2$  test or matched-pairs *t* test were used to compare BP and esophageal pH variables before and after antacid therapy. A difference was considered statistically significant at  $P \leq 0.05$ .

## RESULTS

### General Results

Among the 86 patients with hypertension, 38 patients (44.2%) had GERD (Fig. 1); however, only 24 patients satisfied



**FIGURE 1.** Selection of the study group based on the results of concurrent 24-hour BP and esophageal pH monitoring. GERD indicates gastroesophageal reflux disease; BP, blood pressure; HE, high BP episodes; HE dependent on PR, high BP episodes, with at least 1-episode dependent on pathologic reflux.

the criteria that at least 1 high BP episode was time-dependent on the occurrence of PR (Fig. 1). Of these 38 patients who met GERD and hypertension criteria, 25 patients first showed GERD symptoms and the emergence of hypertension were 1 to 10 years later; 13 patients first showed hypertension and the emergence of GERD were 0.8 to 6 years later. The duration of GERD were (8.2±5.6) years and of hypertension were (6.4±4.0) years. There were no differences in mean age, sex distribution, body mass index (BMI), prevalence of smoking, and antihypertensive drug medication between patients with GERD versus those without GERD ( $P > 0.05$  in all cases). The proportion of patients taking different types of antihypertensive drugs (eg,  $\beta$ -blocker, calcium channel antagonist, angiotensin converting enzyme inhibitor, or angiotensin II receptor blocker) were also comparable in both groups. However, there were no statistical difference in both groups (Table 1).

**Secondary Results**

The incidence of esophagitis was significantly higher in GERD group than the control group ( $P = 0$ ; Table 1). There were 494 PR episodes and 684 high BP episodes in the 38 patients with GERD. Of these, 317 PR episodes and 339 high BP episodes occurred at night, whereas 177 PR episodes and 345 high BP episodes occurred at daytime. The PR episodes were significantly more common at night when supine ( $P = 0.003$ ), occurring predictably around 2:00 AM (Fig. 2). There was no difference between daytime and nighttime in the incidence of high BP episodes ( $P = 0.934$ ), however, there significantly increased during early AM or waking hours than other time periods ( $P < 0.05$ ).

A significantly higher incidence of the high BP episodes was observed in GERD patients than in non-GERD patients [22.58 (SD 6.33) vs. 14.82 (SD 5.44);  $P = 0.016$ ]. GERD patients also had significantly higher average nocturnal BP than non-GERD patients ( $P = 0.026$  and  $P = 0.020$  for systolic BP and diastolic BP, respectively). However, daytime BP and mean BP were not significantly different between patients with and without GERD ( $P > 0.05$ ; Fig. 3). The percentage of reduced nocturnal BP (nondippers) was 6.5%.

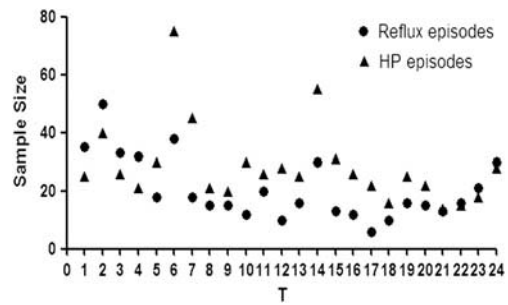
**TABLE 1.** Clinical Characteristic of the Studied Patients

Study Population	n (%)		P
	GERD (-) 48 Patients	GERD (+) 38 Patients	
Age (y)	53.41 ± 9.25	55.32 ± 13.71	0.325
Males	27 (56.25)	22 (57.89)	0.878
Body mass index*	25.70 ± 1.26	24.50 ± 1.39	0.672
Smoking			
Never	20 (41.67)	16 (42.11)	0.967
Former	10 (20.83)	8 (21.05)	0.980
Current	18 (37.50)	14 (36.84)	0.950
Antihypertensive drugs			
$\beta$ -Blocker	24 (50.00)	22 (83.33)	0.466
Calcium channel blocker	18 (37.50)	14 (36.84)	0.950
ACE inhibitor or ARB	12 (25.00)	10 (26.32)	0.890
Esophagitis	0	14	0.00

*P*-values were calculated using the 1-sample Student *t* test.

\*Body mass index was calculated as the weight in kilograms divided by the square of the height in meters.

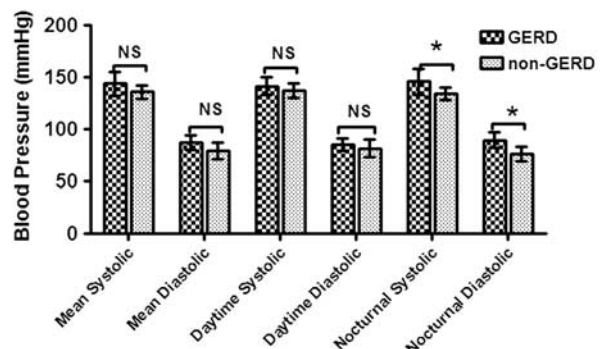
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; GERD, gastroesophageal reflux disease.



**FIGURE 2.** Scatter plot of reflux episodes and high BP episodes among 38 GERD patients during the monitoring period (non-linear regression analyses,  $R^2 = 0.259$ ; x-axis stands for a 24-hour monitoring period, y-axis stands for episodes of 2 variables). GERD indicates gastroesophageal reflux disease; BP, blood pressure; HP, hypertension.

**Primary Results**

Among 38 GERD and hypertension patients, there was correlation in the frequencies of high BP and PR episodes in 24-hour period ( $R^2 = 0.259$ ,  $P = 0.011$ , Fig. 2). Twenty-four patients who at least 1 high BP episode was time-dependent on the occurrence of PR. Two patients had only 1 high BP episodes related to PR, the other 22 patients had at least 2 episodes. Manual correlation of the time of the high BP episodes to the time of the PR episodes revealed 102 (14.9%) high BP episodes to be PR dependent. The 24 patients who high BP episodes related to PR were administered 14 days of PPI therapy with omeprazole (20 mg bid). Esophageal pH parameters of GERD patients gathered before and after treatment with omeprazole are shown in Table 2. As expected, the DeMeester score, the total duration for which pH remained  $< 4$ , the percentage duration for which pH was  $< 4$  in the upright position, the percentage duration for which pH was  $< 4$  in the recumbent position, the number of times pH decreased to  $< 4$ , the number of PR episodes, and the number of PR-dependent high BP episodes were all significantly decreased on the 14th day of the therapy ( $P < 0.05$  in all cases). Omeprazole therapy also resulted in a statistically significant reduction of BP; the mean BP, daytime BP, and nighttime BP were significantly lower after therapy ( $P < 0.05$ ; Table 2 and Fig. 4).



**FIGURE 3.** GERD patients have significantly higher nocturnal BP than non-GERD patients (systolic BP,  $P = 0.026$ ; diastolic BP,  $P = 0.020$ ). \*Significant difference between bars in the same cluster ( $P < 0.05$ ). GERD indicates gastroesophageal reflux disease; BP, blood pressure; NS, not significant.

**TABLE 2.** Results of Esophageal pH Monitoring and BP Monitoring in 24 GERD Patients: Before and After Antacid Therapy

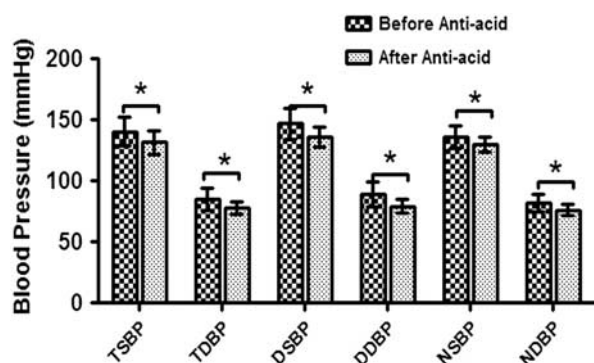
Variables	Before Therapy		After Therapy		P
	Mean	SD	Mean	SD	
DeMeester score	46.82	4.52	28.28	4.66	0.001
TT (min)	2152.63	41.25	718.47	28.56	0.00
UPT (%)	4.16	1.85	2.51	1.17	0.001
SPT (%)	5.74	2.23	3.29	1.85	0.01
PR (n)	28.21	6.22	8.71	3.58	0.00
HE dependent on PR (n)	12.66	5.53	5.78	2.80	0.001
TSBP (mm Hg)	137.50	9.80	130.75	6.62	0.00
TDBP (mm Hg)	82.83	7.29	77.54	5.02	0.001
DSBP (mm Hg)	141.51	9.64	133.50	5.78	0.001
DDBP (mm Hg)	85.38	6.20	79.25	5.12	0.021
NSBP (mm Hg)	137.68	8.88	126.25	9.62	0.00
NDBP (mm Hg)	80.28	7.66	75.83	4.50	0.02

DDBP indicates mean daytime diastolic blood pressure; DSBP, mean daytime systolic blood pressure; GERD, gastroesophageal reflux disease; HE, dependent on PR; high BP episodes, with at least 1 episode dependent on pathologic reflux; NDBP, mean nocturnal diastolic blood pressure; NSBP, mean nocturnal systolic blood pressure; PR (n), number of episodes of pathologic reflux; SPT (%), time percentage of supine position pH <4; TDBP, mean diastolic blood pressure; TSBP, mean systolic blood pressure; TT, total time that pH was <4 during 24-hour pH monitoring; UPT (%), time percentage of upright position pH <4.

## DISCUSSION

This study mainly considers the relationship between GERD and hypertension. The use of 24-hour continuous BP monitoring provides a clear picture of an individual's BP because it is unaffected by the phenomenon of "white coat hypertension"; allows identification of hidden hypertension; can assess degree of arised BP or short-term variations in BP and the circadian rhythm; and so on. Similarly, 24-h esophageal impedance and pH monitoring detects not just acid reflux but also helps distinguish between weak acid reflux and nonacid reflux.

Gastroesophageal reflux (GER) during sleep can lead to the development of extra-esophageal complications such as asthmatic attacks and idiopathic pulmonary fibrosis.<sup>15</sup> A



**FIGURE 4.** Blood pressure in 24 GERD patients before antiacid treatment and at the 14-day follow-up. GERD indicates gastroesophageal reflux disease; TSBP, mean systolic blood pressure; TDBP, mean diastolic blood pressure; DSBP, mean daytime systolic blood pressure; DDBP, mean daytime diastolic blood pressure; NSBP, mean nocturnal systolic blood pressure; NDBP, mean nocturnal diastolic blood pressure. \*Significant difference between bars in the same cluster ( $P < 0.05$ ).

large national survey in the United States that evaluated the prevalence of nocturnal GER and its effect on quality of life found that 10% of respondents have symptoms of nocturnal GER.<sup>16</sup> In a recent prospective study of 331 obstructive sleep apnea patients, nocturnal GER was present in 62% of patients before the start of continuous positive airway pressure treatment.<sup>17</sup> Consistent with previous studies, our study also showed that episodes of GER were more common in the nighttime, especially when supine (Fig. 2). This could be because of increased vagal activity at night, which can increase gastric acid production, delay esophageal clearance, and reduce lower esophageal sphincter tension. In addition, in the recumbent posture, the position of the esophagus and stomach increases the chances of reflux.

The defined of large HH was size of hernia sac > 6 cm, or > 30% of the stomach herniated into the chest cavity.<sup>18</sup> Large HH could compress the left atrium and result in hemodynamic changes.<sup>10</sup> OSAS is defined as an apnea-hypopnea index (AHI) > 5, along with excessive daytime somnolence.<sup>19</sup> The similar epidemiological and biochemical variables raises the possibility of considerable co-morbidity between hypertension and OSAS. The numerous epidemiological datas support a causal relationship between OSAS and hypertension.<sup>20-22</sup> These results led to the exclusion of large HH and OSAS patients.

GERD has been identified in 40% of patients with angiographically proven coronary artery disease,<sup>5</sup> and cardiac arrhythmias have also been found to be significantly correlated with GERD episodes.<sup>7</sup> An earlier study had shown that hypertension occurred more frequently in patients with BE and RE, GERD was associated with an increased prevalence of hypertension.<sup>6</sup> The study underwent at the similar external conditions. So, we did not consider heart rate, and used BP as the only surrogate in pathologic esophageal acid reflux. We used 24-hour esophageal impedance and pH and BP monitoring and found that there was significant association between hypertension and GERD ( $R^2 = 0.259$ , Fig. 2), with episodes of PR being associated with elevation of both systolic and diastolic BP (Fig. 3). Among 684 high BP episodes in the 38 patients with GERD, manual correlation of the time of the high BP episodes to the time of the PR episodes revealed 102 (14.9%) high BP episodes to be PR dependent. This method was arbitrarily selected time window, which could be free of time dependent analysis shortcomings. Although a minority of BP episodes was related to PR, it was important significance to clinical research. Although our findings may be true, the interrelated mechanisms are not known.

The common risk factors for hypertension and GERD are one of the possible explanations for the relationship between these 2 conditions. A higher prevalence of GERD and CAD has been reported in elders, smokers, and patients with excess abdominal fat.<sup>23,24</sup> In our study population there was no significant difference between GERD patients and non-GERD patients in mean BMI or in the distribution of male sex or obesity and so it is unlikely that these factors were responsible for the GER associated with hypertension (Table 1), which was the similar as a previous study.<sup>6</sup>

$\beta$ -Blockers and calcium channel blockers, both of which are commonly used in patients with hypertension, may increase GER by reducing the tone of the lower esophageal sphincter and by diminishing esophageal clearance. This may be one of mechanisms responsible for the relatively high prevalence of GERD in patients with hypertension. Another possible mechanism could be a neural reflex between the

esophagus and the cardiovascular system, with GER causing chest pain, and the reflex sympathetic activity induced by chest pain leading to hypertension. Recently, a new theory has been put forward that could also explain the relationship between GERD and hypertension. The theory postulates that under the regulation of caudal solitary complex neurons, cardiorespiratory and digestive reflexes are activated concurrently by the same stimuli. The most notable of which are hypercapnic acidosis and orexin.<sup>25</sup>

The PPI test is a useful method for the diagnosis and treatment of patients with GERD.<sup>26</sup> Current guidelines advise anti-acid therapy with once-daily PPI for those with typical GERD symptoms (ie, regurgitation, heartburn) and twice-daily PPI for those with extra-esophageal symptoms.<sup>27,28</sup> PPI therapy has shown ability to improve asthma symptoms<sup>29</sup> and performance on pulmonary function tests<sup>30</sup> thus allowing reductions in asthma medications.<sup>31</sup> Short-term, high-dose PPI therapy has also been successful in controlling non-cardiac chest pain.<sup>32,33</sup> Therefore, based on the proven anti-acid effect of PPI, we hypothesized that reduction in GER could be used as an adjunctive therapy for patients with essential hypertension. In this study, we administered 14-day PPI therapy to 24 patients with essential hypertension and assessed how change in esophageal pH affected the BP. Our results clearly demonstrated that antacid drug therapy could reduce systolic and diastolic BP of patients with both GERD and essential hypertension (Table 2 and Fig. 4).

### Study Limitations

This study has several limitations: First, hypertension occurred before or after the start of PR could not be assessed. Second, we did not analyze factors known to increase BP and GERD, such as high alcohol, stress and lifestyle. Third, the study sample was small, which precluded subgroup analysis for different factors. Finally, there was no control group in the second part of the study where PPI treatment was administered; it was not clear whether GERD therapy has long lasting effects on hypertension; the lower BP levels detected post treatment may have been related to decrease stress as the patients had already undergone monitoring previously.

### CONCLUSIONS

This study demonstrated that parts of reflux episodes might be associated with BP elevation. Antacid therapy restored esophageal pH to normal and significantly lowered elevated BP, which suggested that treatment of GERD could be useful for normalizing BP in essential hypertension patients. Multicenter randomized controlled trials are required to confirm our findings and clarify the underlying mechanisms.

### ACKNOWLEDGMENTS

We are indebted to Dr L.X. Gu for assistance with the statistical analysis. The trial has not been registered, because the study is not a randomized controlled trial, and we begin to engage in research in this area recently.

### REFERENCES

- Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high BP: the JNC 7 report. *JAMA*. 2003;289:2560–2572.

- Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365:217–223.
- Storr M, Meining A, Allescher HD. Pathophysiology and pharmacological treatment of gastroesophageal reflux disease. *Dig Dis*. 2000;18:93–102.
- Vakil N, Van Zanten SV, Kahrilas P, et al. Global Consensus Group. The montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006;101:1900–1920.
- Lux G, Van Els J, The GS, et al. Ambulatory oesophageal pressure, pH and ECG recording in patients with normal and pathological coronary angiography and intermittent chest pain. *Neurogastroenterol Motil*. 1995;7:23–30.
- Gudlaugsdottir S, Verschuren W, Dees J, et al. Hypertension is frequently present in patients with reflux esophagitis or Barrett's esophagus but not in those with non-ulcer dyspepsia. *Eur J Intern Med*. 2002;13:369–375.
- Kubota S, Nakaji G, Shimazu H, et al. Further assessment of atrial fibrillation as a risk factor for gastroesophageal reflux disease: a multicenter questionnaire survey. *Intern Med*. 2013;52:2401–2407.
- Sarnelli G, Santonicola A, D'Aniello R, et al. GERD is a protective risk factor for hypertension. Abstracts of the 18th National Congress of Digestive Diseases. *Dig Liver Dis*. 2012;44:S219.
- Liang WT, Wang ZG, Wang F, et al. Long-term outcomes of patients with refractory gastroesophageal reflux disease following a minimally invasive endoscopic procedure: a prospective observational study. *BMC Gastroenterol*. 2014;14:178.
- Oishi Y, Ishimoto T, Nagase N, et al. Syncope upon swallowing caused by an esophageal hiatal hernia compressing the left atrium: a case report. *Echocardiography*. 2004;21:61–64.
- Zhang W, Si L-Y. Obstructive sleep apnea syndrome (OSAS) and hypertension: Pathogenic mechanisms and possible therapeutic approaches. *Ups J Med Sci*. 2012;117:370–382.
- Dobrzycki S, Baniukiewicz A, Korecki J, et al. Does gastroesophageal reflux provoke the myocardial ischemia in patients with CAD? *Int J Cardiol*. 2005;104:67–72.
- Lam HG, Breumelhof R, Roelofs JMM, et al. What is the optimal time window in symptom analysis of 24-hour esophageal pressure and pH data? *Dig Dis Sci*. 1994;39:402–409.
- Kim GH. How to interpret ambulatory 24 hr esophageal pH monitoring. *J Neurogastroenterol Motil*. 2010;16:207–210.
- Pasricha PJ. Effect of sleep on gastroesophageal physiology and airway protective mechanisms. *Am J Med*. 2003;115(suppl. 3A):114S–118SS.
- Farup C, Kleinman L, Sloan S, et al. The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. *Arch Intern Med*. 2001;161:45–52.
- Green BT, Broughton WA, O'Connor B. Marked improvement in nocturnal gastroesophageal reflux in a large cohort of patients with obstructive sleep apnea treated with continuous positive airway pressure. *Arch Intern Med*. 2003;163:41–45.
- Mitiek MO, Andrade RS. Giant hiatal hernia. *Ann Thorac Surg*. 2010;89:S2168–S2173.
- Flemons WW, Buysse D, Redline S, et al. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research The Report of an American Academy of Sleep Medicine Task Force. *Sleep*. 1999;22:667–689.
- Silverberg DS, Oksenberg A, Iaina A. Sleep-related breathing disorders as a major cause of essential hypertension: fact or fiction? *Curr Opin Nephrol Hypertens*. 1998;7:353–357.
- Kales A, Bixler EO, Cadioux RJ, et al. Sleep apnoea in a hypertensive population. *Lancet*. 1984;2:1005–1008.
- Lavie P, Ben-Yosef R, Rubin AE. Prevalence of sleep apnea syndrome among patients with essential hypertension. *Am Heart J*. 1984;108:373–376.

23. Wia S, Tkowski M, Budzynski J, et al. Gastroenterological causes of cardiological symptoms [Gastroenterologiczne przyczyny dolegliwosci kardiologicznych]. *Kardiol Pol.* 2002;57:261–267.
24. Baniukiewicz A, Gabrylewicz A. Gastro-esophageal reflux disease (Part I). Etiopathogenesis, clinical symptoms [Choroba refluksowa przezyku (cze,s'c' I). Etiopatogeneza, objawy kliniczne]. *Pol Arch Med Wew.* 1994;92:507–512.
25. Dean JB. Theory of gastric CO<sub>2</sub> ventilation and its control during respiratory acidosis: Implications for central chemosensitivity, pH regulation, and diseases causing chronic CO<sub>2</sub> retention. *Respir Physiol Neurobiol.* 2011;175:189–209.
26. Tutuian R. Update in the diagnosis of gastroesophageal reflux disease. *J Gastrointestin Liver Dis.* 2006;15:243–247.
27. Williams RB, Szczesniak MM, Maclean JC, et al. Predictors of outcome in an open label, therapeutic trial of high-dose omeprazole in laryngitis. *Am J Gastroenterol.* 2004;99:777–785.
28. Park W, Hicks DM, Khandwala F, et al. Laryngopharyngeal reflux: prospective cohort study evaluating optimal dose of proton-pump inhibitor therapy and pretherapy predictors of response. *Laryngoscope.* 2005;115:1230–1238.
29. Kiljander TO, Salomaa ER, Hietanen EK, et al. Gastroesophageal reflux in asthmatics: a double-blind, placebo-controlled crossover study with omeprazole. *Chest.* 1999;116:1257–1264.
30. Harding SM, Richter JE, Guzzo MR, et al. Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med.* 1996;100:395–405.
31. Irwin RS, Curley FJ, French CL. Difficult-to-control asthma. Contributing factors and outcome of a systematic management protocol. *Chest.* 1993;103:1662–1669.
32. Botoman VA. Noncardiac chest pain. *J Clin Gastroenterol.* 2002;34:6–14.
33. Juul-Hansen P, Rydning A, Jacobsen CD, et al. High-dose proton-pump inhibitors as a diagnostic test of gastro-oesophageal reflux disease in endoscopic-negative patients. *Scand J Gastroenterol.* 2001;36:806–810.