

Diltiazem as a novel therapy for a chronic cough subtype

Keith R. Conti BS. ¹ Ronak Modi MD. ² Aaron Jaworek MD. ³

1. Temple/St. Luke's School of Medicine, Bethlehem, PA. 2. St. Luke's Gastroenterology Specialists, Bethlehem, PA. 3. Specialty Physician Associates, Bethlehem, PA

Chief Complaint

Chronic cough

History of Present Illness

A 72-year-old woman with past medical history significant for exercise induced asthma, and environmental allergies presented to tertiary referral laryngology office with persistent dry cough that had started with upper respiratory tract infection (URTI) 3 years ago. Upon completion of antibiotics for URTI, all symptoms resolved except for the cough. Cough was triggered by sitting in the car and getting out of bed in the morning. Not triggered by exercise, cold air, talking/laughing, meals, or during sleep. She quit smoking 45 years ago.

Treatment trials for cough:

- Lansoprazole 60mg qam – stopped, no benefit
- Pantoprazole 40mg qam, ranitidine 300mg qhs – no benefit, currently weaning
- Gabapentin up to 600 BID – stopped, benefit waned
- Allergy/asthma therapy (including 1st gen. antihistamine, decongestant trial, multiple inhalers) managed by allergist and pulmonologist
- Benzonatate – no benefit
- Prednisone – benefit
- Speech-language pathology for cough therapy – benefit

Cough symptom index (CSI) = 7

Reflux symptom index (RSI):

- Before starting pantoprazole and ranitidine = 27
- One month after treatment = 18 (5 for hoarseness and cough responses)

Physical Exam

Voice: mild raspy, dec volume

Neck/Thyroid: Approx. 1 cm palpable isthmus nodule **Stroboscoped laryngoscopy:** mild reflux laryngitis (RFS = 11), mild right vocal fold paresis, and slightly decreased laryngeal adductor reflex responses bilaterally. (**Images 1 and 2**)

Remaining head and neck exam was unremarkable.

Diagnostic Testing

Esophageal high resolution manometry (Figures 1-3):

- Complete bolus transit: liquid = 80% (wnl), viscous 50% (low).
- **Distal Contractile Integrals (DCI) > 8000 mmHg*s*cm in 5 of 10 swallows**
- **Integrated Relaxation Pressures (IRP) wnl**

24-Hour Multichannel Intraluminal Impedance (MII) with Dual pH Sensors on PPI/H2B:

- 42 reflux events, 12 acid (pH<4), 6 of 8 supine events acid
- 3 upright acid reflux events were proximal
- 10 of 33 coughs correlated with reflux, 1 acid
- Symptom index (SI) = 30%
- Symptom association probability (SAP) = 100%.

Chest x-ray: normal

Labs: normal – TSH, free T4, ANA, RF, Mycoplasma titer, Lyme titer, FTA-ab, Gluten sensitivity panel

Fractional Exhaled Nitric Oxide (FENO): 11 (normal)

EGD with biopsies (duodenum, stomach): normal

Thyroid ultrasound: multiple nodules, no FNA indicated

Investigative Studies

Image 1: Larynx with vocal folds adducted



Image 2: Larynx with vocal folds abducted

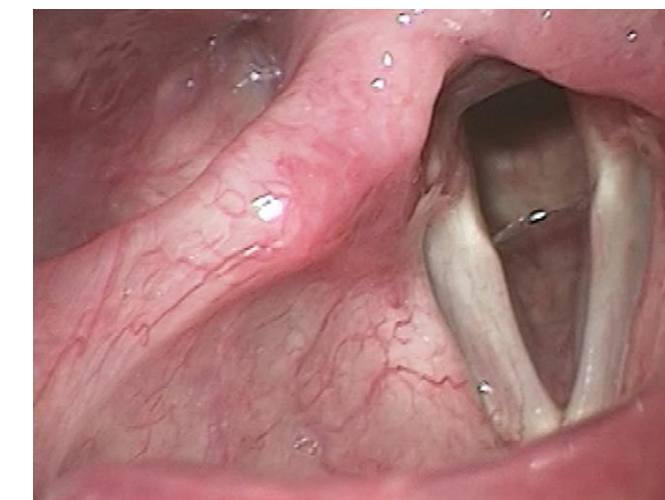


Figure 1: Esophageal High Resolution Manometry (HRM) with elevated DCI

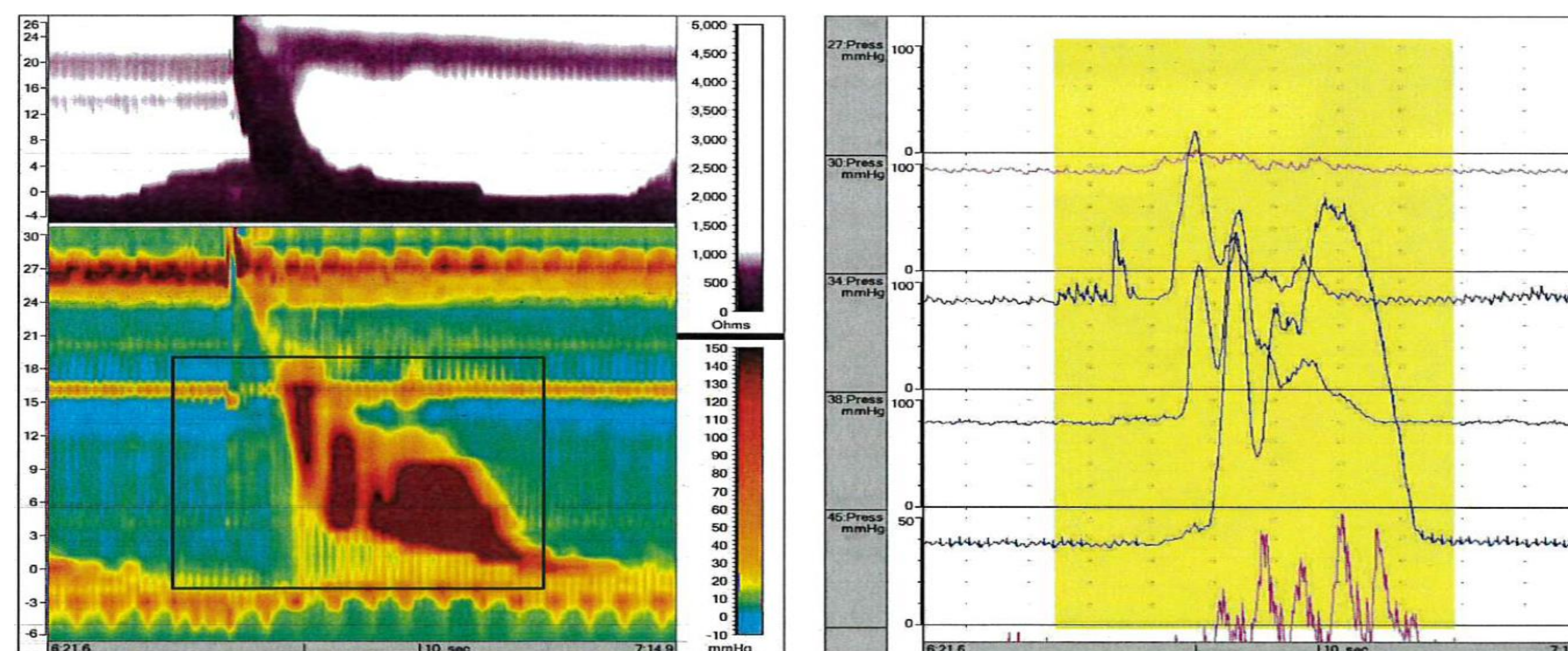


Figure 2: Distal Contractile Integral (DCI) for 10 Swallows

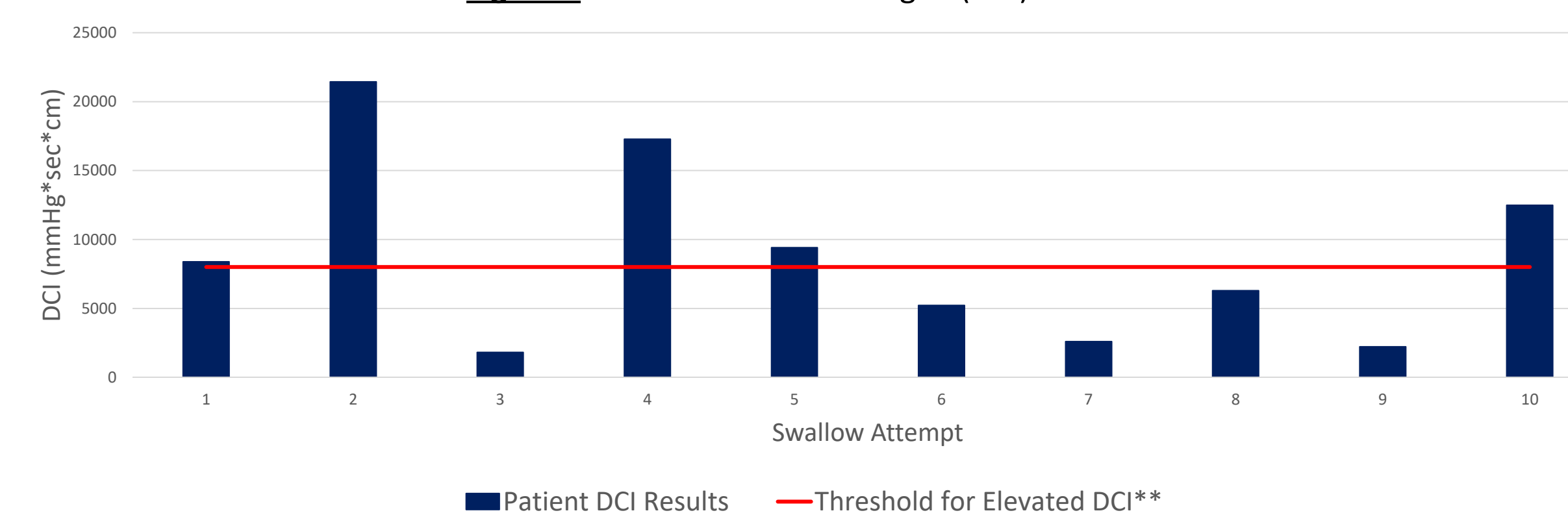
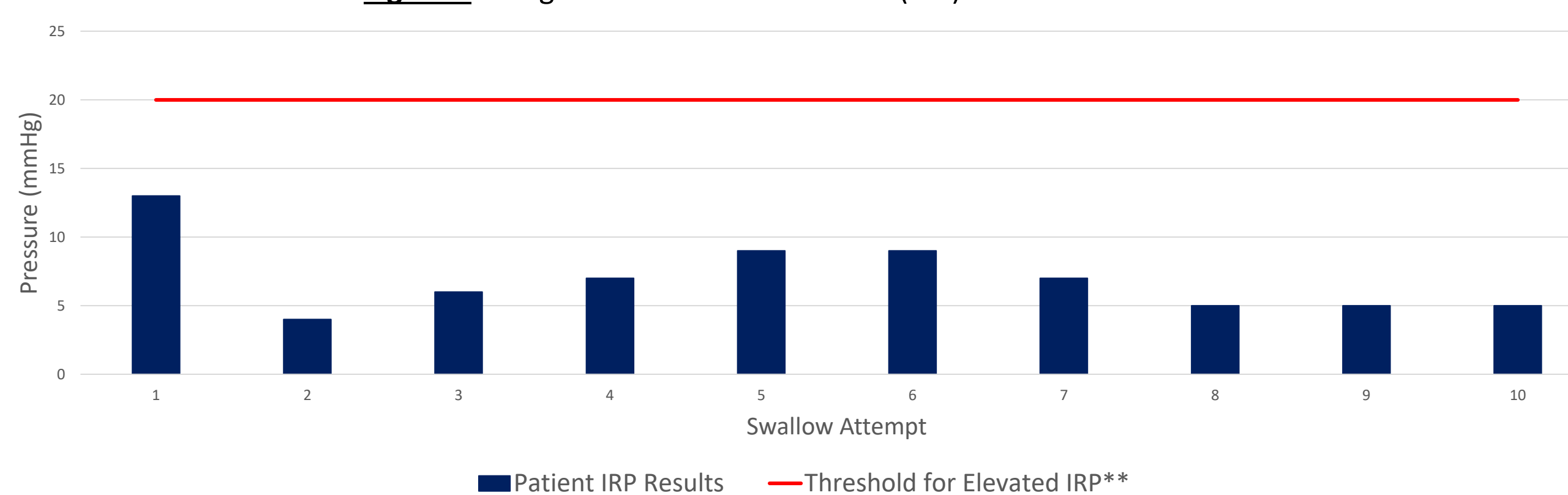


Figure 3: Integrated Relaxation Pressure (IRP) for 10 Swallows



Results/Discussion

This patient's chronic cough resolved upon initiation of diltiazem, a calcium channel blocker (CCB), to treat hypercontractile esophagus (HE). Chicago classification for HE is defined as having at least two swallows on HRM with DCI ≥ 8000 mmHg*s*cm while the IRP remains < 20mmHg (normal IRP for Sandhill <20mmHg).

Diltiazem is a non-dihydropyridine (non-DHP) CCB that alters both vascular smooth muscle and cardiac muscle function. Commonly, it is used to treat a variety of cardiovascular diseases including angina, hypertension, and cardiac dysrhythmias. Typically, CCBs are avoided as much as possible in patients with GERD due to their effects on relaxation of the lower esophageal sphincter (LES). Despite this observation, a study by Hughes, et al. showed that DHP CCBs were associated with a 2.7-fold increase in reflux symptoms compared to non-DHP CCBs like diltiazem. Moreover, new reflux symptom development and reflux symptom exacerbation occurred least with diltiazem.

After following standard chronic cough diagnostic algorithms first, treatment with a CCB was indicated in this case given the concomitant diagnosis of HE. As a result, more invasive interventions such as anti-reflux surgery and therapeutic injection trials were avoided.

Conclusion

We present, to our knowledge, the first case of chronic cough with hypercontractile esophagus treated with the CCB diltiazem. Historically, CCBs have been implicated in worsening GERD by decreasing LES tone. As a result, chronic cough due to reflux may be exacerbated by CCB use. When chronic cough is accompanied by HE confirmed with HRM, a trial of diltiazem may be considered as a therapeutic option with the least potential for LES hypotonicity.

Clinical Pearls

1. Despite the most common causes of chronic cough accounting for up to 90% of patients: upper airway cough syndrome (UACS), reflux, asthma/non-asthmatic eosinophilic bronchitis (NAEB), ACE inhibitor use, and cigarette smoking – a variety of atypical causes remain
2. Chronic cough management often requires a multidisciplinary team approach
3. A trial of the CCB diltiazem may be considered in patients with chronic cough accompanied by HE diagnosed with HRM.

References

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