Low Esophageal Mucosal Blood Flow in Patients with Nutcracker Esophagus

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RKM: Conceived the project, designed experiments, data acquisition, data analysis and wrote the manuscript

YJ: Experimental design, data acquisition, data analysis, figures creation and help with manuscript writing

Title: Short title: Esophageal ischemia in Nutcracker Esophagus
**ABSTRACT**

**Background & Aims:** Nutcracker Esophagus (NE) is characterized by high amplitude peristaltic esophageal contractions and these patients often present with symptoms of “angina like” or non-cardiac chest pain (NCCP). Tissue ischemia is a known cause of visceral pain and the goal of our current study was to determine if esophageal wall blood perfusion (EWBP) is reduced in patients with NE. **Methods:** Fourteen normal subjects (mean age 51 yrs, 11 males) and 12 patients (mean age 53 year, 9 males) with NE and NCCP were investigated. The EWBP was measured continuously using a custom designed laser Doppler probe tethered to a Bravo capsule, which anchored it to the esophageal wall. **Results:** The baseline EWBP in normal subjects was 651±27 perfusion units (PU). In patients with NE the baseline EWBP was significantly lower than in the normal subjects (451±32 PU). The EWBP decreased after injection of edrophonium (that increases muscle contractions) and increased following sublingual nitroglycerine (NTG) administration (that relaxes muscle) in normal subjects as well as in NE patients. Spontaneous pain events during the recording period were often associated with drops in the EWBP. **Conclusions:** We propose that low EWBP leads to hypoxia of the esophageal tissue, which may be a mechanism of esophageal pain in patients with NE.

**Keywords:** Esophageal wall blood perfusion, ischemia-perfusion injury; esophageal pain; non-cardiac chest pain
INTRODUCTION

“Angina like” non-cardiac esophageal chest pain (NCCP) is extremely common; 25% of adults may suffer from it(5). It is one of the most common causes of visits to the medical emergency room. These patients often undergo extensive cardiac testing to rule out coronary artery disease and consume large amount of health care resources. Motor disorders of the esophagus are a known cause of “angina like” chest pain, however, the precise relationship between abnormal motility and pain is not known. Work conducted during 1980’s and 1990’s focused on the high amplitude contractions (nutcracker esophagus) as a mechanism of esophageal pain, however, prolonged esophageal motility and pH recordings revealed poor correlation between pain events and high amplitude esophageal contractions(16, 29, 30). Work conducted since then suggests that the esophageal pain is related to “hypersensitivity” of the esophagus, which implies that a number of stimuli, i.e., contractions, distension(31), acid and possibly other factors that do not elicit pain in normal subjects do so in patients(6, 20, 26). Esophageal hypersensitivity is also referred to as allodynia and hyperalgesia.

Several investigators have suspected ischemia of the esophageal wall as a possible mechanism of esophageal pain. MacKenzie et all studied re-warming rate of perfused water in the esophagus as a measure of esophageal wall blood flow and found it to be lower in patients with esophageal pain compared to normal subjects(22). We recently reported the relationship between EWBP and esophageal muscle contraction in normal healthy subjects using a novel laser Doppler technique. We found that contraction of the circular and longitudinal muscle of the esophagus reduce esophageal mucosal perfusion(24),(17). The goal of our current study was to determine EWBP in patients with “nutcracker esophagus” (NE), an esophageal motility disorder associated with NCCP. We measured EWBP using the laser Doppler technique under baseline
condition and following administration of pharmacologic agents that are often used to induce and relieve esophageal pain.

**Methods & Experimental Design**

**Subjects:** Studies were conducted in 14 healthy volunteers (mean age = 51 years, 11 M) and 12 patients (53 years, 9 M) with NE and NCCP. Patients were recruited from the esophageal clinic/GI function laboratory at the University of California San Diego (UCSD). Cardiac etiology of pain was excluded by appropriate standard of care testing in each subject, prior to their inclusion in the study. All patients had a prior esophageal high resolution esophageal manometry (HRM) study with the diagnosis of high amplitude contractions (NE, mean contraction amplitude of > 180mmHg in the distal esophagus). These patients had also failed a trial of acid inhibition therapy, i.e, double-dose proton pump inhibition (PPI) therapy. An important inclusion criterion for our study was the presence of frequent/daily chest pain symptoms. Protocol for the studies was approved by the “University of California San Diego Institutional Review Board for the Protection of Humans”. Subjects fasted and stopped smoking for 6 hours prior to the study.

**Monitoring Technique:** The EWBP was monitored using a custom designed laser Doppler probe (Periflux system 5000, AB, Box 564 SE-175 26 JärFälla, Stockholm, Sweden) anchored to the esophageal wall (figure 1 A & B) as described previously(17). Briefly, the Laser Doppler probe was firmly taped to a Bravo pH capsule using paraffin film (figure 1 B). The laser beam exits from the laser Doppler probe in the direction and at the level of the suction cup of the Bravo pH capsule. The laser Doppler signal was calibrated *in-vitro* using PF 1001 calibration device (0-250 PU) (from Perimed) prior to placement in each subject. In majority of subjects, laser Doppler probe was first passed through the nose and pulled out from the mouth. It was
then taped to the side of the Bravo pH capsule and assembly was then introduced through the mouth into the esophagus. Bravo capsule was deployed at 5 to 6 cm above the lower esophageal sphincter (LES). Following placement of the Bravo pH capsule and laser Doppler catheter probe, a high resolution manometry (HRM) catheter (Sierra Scientific, Los Angeles, CA) was passed through the nose and placed into the esophagus. Thus, simultaneous and continuous recordings of the esophagus, LES & stomach pressures, esophageal pH and esophageal wall blood perfusion (EWBP) were obtained. All recordings were synchronized manually using event markers on the 3 recorders (laser Doppler, pH and HRM).

**Experimental Design:** Following an accommodation period of 10 minutes, 8 - 10 wet swallows (5 ml water) were recorded. A baseline period of 50-60 minutes was then recorded, following which subjects ate a standard 1000 Kcal meal. Recordings were performed for several hours, at the end of which edrophonium hydrochloride (tensilon, 80 µg/kg) was injected as an I.V. bolus(19). Ten minutes after tensilon injection subjects received sublingual nitroglycerin (NTG, 0.4mg) and recordings were performed for another 10 minutes. The total study period ranged from 3-8 hours per subject, depending upon the subject’s tolerability and the detachment of laser probe from the Bravo capsule. Blood pressure was monitored continuously following tensilon and NTG administration. At the end of the study, the laser Doppler probe was pulled out by applying a gentle tug to the catheter, which detached it from the Bravo pH capsule.

**Data Analysis and Statistics for EWBP**

In addition to the laser Doppler perfusion units (PU), laser Doppler monitor also provides a continuous record of the total backscatter (TB) values. The TB is a reading of the amount of light reflected back to the laser Doppler probe. A TB signal reading of $\geq 1$ indicates adequate contact between the Doppler probe and esophageal mucosa. Mean EWBP values during 50-60
minute baseline period before meal represented the baseline EWBP value. These time periods included spontaneous contractions. The effect of edrophonium on EWBP was determined by comparing the values under 400 PU during 5 minutes before and 5 minutes after the injection. Similarly, mean EWBP values 5 minutes before and 10 minutes after NTG administration was determined. In addition to EWBP, the manometry record was assessed for any abnormal esophageal contractions, including contractions of ≥ 180 mmHg and simultaneous contractions during 2 minutes prior to the onset of pain. Esophageal pH recordings were scored for reflux events (pH < 4). Data are reported as mean ± standard error of mean (SEM). Data were analyzed using one-way ANOVA (parametric and nonparametric) and Student’s paired or unpaired t-test, as appropriate. Statistical significance = p < 0.05.

**Results**

**Patient Demographics**

14 normal subjects (11 men, median age 50 years (35 to 59 years) and 12 patients with NE, (9 men, median age 49 years (35 to 74 years) participated in the study. Majority of our patients reported continuous symptoms (pain/heartburn) during the study. In addition to continuous pain some patients also described increase in symptoms during the study. Three patients did not report any pain during the study and in others there were only brief episodes of pain in the absence of continuous pain during the study, as shown in table 1.

**Esophageal Wall Blood Perfusion**

Figure 1C is an example of the baseline EWBP recording superimposed on the esophageal HRM recording from a normal subject; note the baseline EWBP value of approximately 800 PU, which drops significantly with each swallow-induced contraction to less than 250 PU. Figures 2A, B and C show recordings from three different patients; these patients had continuous
pain/heartburn symptoms during the entire recording periods. In all 3 patients the baseline EWBP values were extremely low (253, 347 and 403 PU) compared to normal subjects and remained low during the majority of the recording time. Unlike normal subjects, where each esophageal contraction caused a prominent drop in the EWBP value, the effect of esophageal contractions on EWBP was variable in the patients, presumably because of the low baseline EWBP value. Some subjects showed a small reduction (Figure 2A) or no change with esophageal contractions and others revealed large fluctuations (Figure 2B) in EWBP following contraction. Figure 3A & B show that mean EWBP was significantly lower in patients compared to normal subjects (451 ± 32 vs 651 ± 27 (P=0.004). However, there is some overlap between NE patients and normal subjects. Figure 3B shows the frequency histogram of the EWBP in normal subjects and NE patients, the curve in patients is shifted to the left, thus proving chronically lower perfusion values in the NE patients compared to normal subjects.

In 3 NE patients, the EWBP measurements were repeated several months apart. In patient 1 the two studies were done one year apart with no change in symptoms during this period, his perfusion values were 358 and 353PU. In patient 2, studies were conducted 2 years apart during which time the patient was treated with botox injections with some improvement in symptoms; his perfusion values improved from 365 to 446 PU. In patient 3 the two studies were conducted 3 months apart, this patient’s pain improved significantly with diltiazem-SR, 240mg/day; his perfusion values were 418 and 508 PU on the 2 study days.

The effects of a meal on the EWBP values are shown in figure 4. In normal subjects the EWBP values increased significantly after the meal (p<.02). On the other hand, meal had no effect on the EWBP of patients with NE, p=0.147

**Effect of Tensilon on EWBP**
As expected, esophageal contraction amplitude and durations were increased by tensilon administration. The EWBP was lower after tensilon compared to before injection in all subjects. Furthermore, percent time perfusion values < 400 PU was greater in NE patients compared to normal subjects (Figure 5).

**Effect of Nitroglycerine on EWBP:**

The 9 normal subjects and all 12 NE patients received sublingual 0.4mg NTG. The typical effect of NTG on the EWBP in one normal subject is shown in figure 6. The NTG did not affect blood pressure but it caused an increase in EWBP values in both normal subjects and NE patients. The mean increase in EWBP was 83 and 53 perfusion units in normal subjects and NE patients respectively (figure 6). Four patients who had no symptoms prior to NTG administration, in other patients who complained of pain prior to NTG, it disappeared in 3 patients, improved in 4 and there was no change in 1.

**Spontaneous Pain Events during the Recording:** some patients described increase in pain, superimposed upon the continuous pain or in the absence of continuous pain during the study period. Some but not all of these pain events were associated with further drops in perfusion values as shown in table 1. In spite of clear instructions to the patients, majority of patients did not describe discrete onset and cessation of pain during the recording period and therefore we could not determine precise relationship between changes in EWBP and pain during all events.

**Manometry and pH before the Pain Events:** In 2 subjects with continuous pain symptoms esophageal pH was low for extended period of time. In the remainder, the esophageal pH was greater than 4 and no acid reflux event was identified during the entire monitoring period. Manometry recordings were evaluated for esophageal contractions of >180mmHg during the 2 minutes window prior to the increase in pain (both in the setting of continuous pain or no
continuous pain); six patients reported such events. High amplitude esophageal contractions were seen in association with 19 of the 35 such events (median 4, range 1-9 pain events/subject). In the other 16 events either no contraction or relatively normal looking contraction was observed. Examples of these events are shown in the figure 7.

**Discussion**

The laser Doppler perfusion technique provides average blood perfusion values in the area of tissue illuminated by the laser light beam (21). It registers blood flow values in perfusion units (PU) rather than the actual volume of blood flow and therefore is ideally suited to measure relative changes in the blood flow. Since the Doppler probe was calibrated *in-vitro*, prior to placement in each subject it is reasonable to assume that the comparison of baseline values among different subjects is valid. The depth of the penetration of the laser beam is generally accepted to be 1-2 mm but in the gastrointestinal application it can be up to 5 mm (18). The depth of penetration depends upon several factors, 1) darker tissue generally has a lesser depth of penetration compared to white or transparent tissue and 2) reduction in the blood perfusion of tissues makes them relatively more transparent and therefore increases the depth of penetration. We observed that the total backscatter (TB) values, a measure of the laser light returned to the Doppler probe increased during manometrically identified contractions.

This is the first study to measure EWBP using a unique method, in which we anchored a laser Doppler probe to the esophageal wall (17), in the NE patients. This assembly is crucial for obtaining artifact free continuous recordings of the EWBP. However, this is not the first study to implicate low EWBP as a possible mechanism of esophageal pain. MacKenzie *et al.* (22) found significantly longer warming rate of injected water into the esophagus (as a measure of EWBP) in 9 patients with esophageal spasm compared to 20 controls, and proposed esophageal wall
ischemia as the cause of pain symptom. Gustafsson et al. (11) used a computerized thermistor recording and found an increase in the mucosal blood flow during acid infusion into the esophagus in patients responding to acid-infusion with heartburn. They also studied patients who responded to edrophonium injection with/without pain (a provocative test that increases the strength and intensity of muscle contractions and esophageal pain)(12) and no difference in the re-warming rates was detected between pain-positive and pain-negative patient groups. We suspect that the use of thermistor technique is not ideal to study EWBP because retention of even a small amount of water in the esophagus due to poor clearance may affect esophageal re-warming significantly. Furthermore the thermal capacity of thermister is large and may be incapable of detecting subtle changes in the EWBP. More recently, Hoff and colleagues(13-15) used the laser Doppler perfusion monitoring to determine distension-related esophageal pain and found that esophageal wall stress and strain, rather than mucosal ischemia is the cause of distension related pain. It is not clear though if they monitored adequacy of contact between the laser Doppler probe and mucosa during their study using total backscatter values.

Even though our laser Doppler recording technique measures esophageal mucosal perfusion we suspect it is representative of blood perfusion in the entire wall of the esophagus, i.e., submucosa and muscularis propria. Our reasoning is that the blood vessels traverse through muscle layers to reach the esophageal mucosa. In our earlier studies in normal subjects, we found that circular and longitudinal muscle contractions of the esophagus reduce esophageal mucosal perfusion(24), which is similar to the concept that blood perfusion to the myocardium occurs during diastole rather than systole. In normal subjects, the duration of reduction in EWBP is relatively brief and is similar to the duration of muscle contraction. A continuously low baseline EWBP value unrelated to manometrically identifiable contractions was an unexpected finding in
our current study of the NE patients. The reasons for low baseline EWBP may be several, 1) all
types of intra-luminal manometry registers circular and not the longitudinal muscle
contraction(25). Furthermore, both circular and longitudinal muscles of the esophagus have
sustained tone, which is not identifiable by manometry. Therefore, it is possible that patients
with esophageal pain have esophageal contractions that are not identified by the HRM. 2) All
types of spastic motor disorders, i.e., achalasia, diffuse spasm, nutcracker esophagus and non-
specific motor disorders have a thicker muscularis propria/muscular hypertrophy (4, 25). Left
ventricular hypertrophy is well known to be associated with ischemia of the myocardium and
cardiac pain (3, 23), it is very possible that esophageal muscle hypertrophy leads to a low blood
flow state of the esophageal wall that causes the symptoms of chest pain in the NE patients.

We expected to find discrete pain events with discrete drops in blood perfusion in all of
our patients for all spontaneous pain events, which we indeed saw in association with several but
not all pain episodes. In addition, there were also periods of sharp drop in perfusion values
during which patients did not report pain. Based on the above, one may argue that we have not
demonstrated a tight relationship between pain and low blood perfusion, which is true. However,
we believe that there are several reasons for the above, 1) it is well known that patients do not
report symptom precisely and accurately and thus it is difficult to demonstrate close temporal
correlation between the pain and reduction in wall perfusion, 2) in the setting of an already
continuous low perfusion it was difficult at times to discern discrete changes in the EWBP, 3)
tissue hypoxia is more likely to be related to the degree and duration of low perfusion and
precise strategy how one can quantitate low perfusion has not been still established and finally,
4) it is possible that different patients have different threshold for hypoxia related tissue injury
and pain.
Myocardial ischemia causes angina and in some cases “dyspepsia and heartburn like symptoms”. Studies by Longhurst et al, spanning over 30 years, show that intestinal ischemia results in generation of lactic acid(27), bradykinin(32), histamine(9), serotonin(10), prostaglandins(8), endothelins(7) and possibly other chemicals that are potent stimuli of the nociceptive nerve endings of the sympathetic nervous system(7). Grundy reported activation of both spinal and vagal visceral nerve endings in response to intestinal ischemia(2). In our earlier studies, we found strong temporal correlation between esophageal pain(1), and heartburn(28) with the sustained longitudinal muscle contraction of the esophagus. We propose that the mechanism by which long duration longitudinal muscle contraction induces pain may be related to the long duration reduction in the EWBP. Edrophonium (tensilon) is a provocative agent to induce esophageal pain and we observed that it causes a fall in the EWBP. On the other hand, NTG is often used to relieve esophageal pain and we found that it increases the EWBP. Therefore, both tensilon and NTG data support our hypothesis that low EWBP may be an important mechanism of esophageal pain.

There are several limitations of our study: 1) how can we be sure that esophagus was indeed the cause of NCCP in our patient population? Cardiac etiology of pain was excluded in all of our patients and none were responsive to what is considered as the adequate acid inhibition therapy. Esophageal manometry revealed evidence of high amplitude contraction that is considered to a marker of esophagus pain in the NE patients. 2) We studied small number of patients with severe symptoms, which is not representative of the bigger population of NCCP patients seen in the clinics and emergency rooms with “angina like” esophageal pain. Our current technique of EWBP can only be performed in the clinic/hospital setting because the laser Doppler monitor is relatively bulky. Esophageal symptoms usually are intermittent and
measurement would require ambulatory long term EWBP monitoring, like pH monitoring, that is not currently available. How hypoxic injury induces NCCP can’t be fully determined from our study.

In summary, it is possible that similar to myocardial hypoxia that causes angina, NCCP is related to low EWBP which leads to activation of the hypoxic pathway culminating in activation of nociceptive nerve terminals in the esophagus. Improvements in the EWBP technique are needed to study a larger number of patients in the ambulatory setting (similar to pH/Bravo pH techniques) to determine if NCCP and heartburn non-responsive to PPI therapy are indeed related to low EWBP and activation of the chronic hypoxia/ischemia perfusion pathway. Furthermore, we anticipate that identification of hypoxia generated factors in the esophageal wall that could be the cause of pain and muscle dysfunction will result in better therapeutic strategies for this extremely prevalent condition.

Acknowledgements

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Figure Legends

Figure 1: A shows the endoscopic picture of actual Bravo and Laser Doppler probe assembly anchored to the esophageal wall in a patient.

1B shows schematic of the laser Doppler probe and Bravo.

1C Esophageal wall perfusion recording in a normal subject: Laser Doppler probe was anchored to the esophageal wall 5 cm above the LES. Esophageal wall perfusion recording is superimposed on the high resolution manometry (HRM). Note, the baseline esophageal blood perfusion (EWBP) of 800 perfusion units (PU) and with each esophageal contraction there is a drop in the EWBP to approximately 250 PU.

Figure 2A, B & C: Esophageal wall perfusion and HRM in 3 patients with continuous pain
These 3 recordings were obtained from 3 different patients with continuous symptoms of either chest pain (A) or heartburn (B and C). Note that the baseline EWBP is low in each of these patients compared to normal subject shown in figure 1C. Also note, unlike normal subject the change in EWBP associated with esophageal contraction was quite variable.

Figure 3 A & B: Baseline EWBP in normal subject and patients
Mean baseline EWBP is significantly lower in patients compared to normal subjects. * = p < .05. The frequency histogram shows that the EWBP curve is shifted to the left in patients suggesting lower perfusion values.

Figure 4: Effect if meal on the EWBP in normal subjects and Nutcracker Esophagus patients. Note, an increase in perfusion values following meal in normal subjects but not in the patients.

Figure 5: Effect of Edrophonium hydrochloride (Tensilon) on the EWBP in Nutcracker Esophagus patients. EWBP recording is superimposed on the HRM record. Note low baseline
ESWP value and the drop with each contraction. Mean data from patients shows lower perfusion values following injection of Tensilon.

**Figure 6: Effect of NTG on the EWBP in a normal subject:** Note, injection of tensilon in this normal subject resulted in reduction in the EWBP and interestingly it induced chest pain. Also note that sublingual NTG increase EWBP and reduced pain. Graphs show the effects of NTG in control and patients.

**Figure 7: Laser Doppler Perfusion Recording Superimposed on the High Resolution Esophageal Manometry during Spontaneous Pain Events:** Four episodes of spontaneous pain events in four different subjects are shown in this figure. Note, that each of these pain event is associated with a drop in the esophageal perfusion of various amplitudes. Also note, that some of these pain events are associated with high amplitude esophageal contractions A, C and D and the one shown in B is not.

Table 1

**REFERENCES**


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<th>Sex</th>
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P = 0.004

Esophageal Wall Perfusion (PU)

Normal n=14

PT n=12

% Frequency Distribution

PU
% PU under 400

Before and after Tensilon

Before

After

P = 0.003

Perfusion Units

Pressure (mmHg)

UES

LES

30 sec