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Noncardiac Chest Pain: The Use Of High Resolution Manometry As A Diagnostic Tool

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NONCARDIAC CHEST PAIN:
THE USE OF HIGH RESOLUTION MANOMETRY AS A DIAGNOSTIC TOOL

by

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ABSTRACT

Chest pain is one of the most common symptoms responsible for emergency department and primary care office visits in the United States. Chest pain can be noncardiac and may be attributed to multiple causes. Esophageal disorders including reflux, motility and functional conditions, affect a large proportion of patients with NCCP and lead to significant morbidity. The use of HRM has changed the diagnostic approach to esophageal motility disorders. It is the most specific and sensitive test for diagnosing motor disorders and a promising procedure in detecting dysmotility disorders in patients with NCCP. Despite the increased sensitivity of HRM, the main indications for esophageal manometry exclude NCCP.

This study assessed the percentage of undiagnosed esophageal motility disorders in patients with NCCP referred for high resolution manometry. Differences in HRM findings in patients with NCCP versus patients meeting AGA recommendations for the clinical use of esophageal manometry were also compared. A retrospective descriptive design was utilized. Two hundred-nineteen patient charts were reviewed. One hundred sixty-eight (77%) patients underwent HRM and met AGA recommendations for esophageal manometry; 51 (23%) patients underwent the procedure after receiving a NCCP diagnosis.

Findings showed that 116 (69%) patients in the AGA group had abnormal findings while 52 (31%) did not. In the NCCP group 34 (67%) had abnormal findings compared to 17 (33%) who did not. To compare normal and abnormal HRM findings in patients with NCCP versus those meeting AGA criteria, Chi-Square analysis was performed between the groups. The results were not statistically significant ($p = 0.10$).

There were no significant differences in the results of HRM in both groups indicating the findings on HRM are the same despite the indication for the procedure. The findings support the use of HRM as a diagnostic tool in patients with chest pain after cardiac workup and endoscopic evaluation. This indicates a possible need to update the AGA indications for esophageal manometry and increase the awareness among healthcare providers regarding the use of HRM in patients with chest pain. Implication for future research is also discussed.

This doctorate thesis is dedicated it to all my family for their love, endless support and encouragement. It is also dedicated to the memory of my beloved father, Tawifiq Hilal, an outstanding teacher and motivator. I would never have gotten so far without his encouragement and belief that I can succeed in everything I do.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER ONE: INTRODUCTION

Noncardiac chest pain (NCCP) is common in the general population (Fass & Achem, 2011). Almost 64% of patients presenting with chest pain are ultimately found to have NCCP as a cause of their symptoms (Eslick, Coulshed, & Talley, 2005). The most recent data obtained from the Centers for Disease Control and Prevention (CDC) suggests that over 11 million patients with unspecified chest pain were seen in all ambulatory settings in 2009 (V. Beresovsky, personal communication, October 26, 2011). This includes patients seen in hospital emergency departments, hospital outpatient departments, physician offices, and clinics. These data are presented in Table 1.

Noncardiac chest pain can also be a chronic condition and often has a benign course and does not increase a patient's mortality rate (Fass & Dickman, 2006; Richter, 1992). On the other hand, NCCP results in high healthcare utilization and significant work absenteeism; it can negatively impact patients' quality of life (Fass & Achem, 2011). Patients with the condition can have a history of multiple hospital admissions and frequently receive unsatisfactory diagnoses despite multiple cardiac diagnostic workups and endoscopic evaluations (Leise et al., 2010). NCCP patients are sometimes discharged from the hospital when signs and symptoms abate but without a defined treatment plan or diagnosis (Eslick et al., 2005). After discharge, continuing care can also be problematic as many of these patients continue to receive care by cardiologists or primary care physicians without an appropriate diagnosis or determined cause for their chest pain (Leise et al., 2010).

Noncardiac chest pain may be attributed to multiple gastrointestinal, musculoskeletal, pulmonary and psychological causes (Leise et al., 2010). Esophageal disorders including reflux, motility, and functional conditions affect a large proportion of patients with NCCP and lead to significant morbidity (Lazarescu, 2008).

Table 1: Number and Percent of Visits to Different Ambulatory Settings by Patients with Diagnosis of Chest Pain in 2009

Ambulatory Setting	Visit (N)	Visit (SE)	Visit (%)	SE (%)
Other chest pain '786.59'				
All ambulatory settings	2,486,196	373,642	0.2	0.03
Physician offices	1,444,121	358,285	0.14	0.03
Hospital Outpatient Departments	*	...	*	...
Hospital Emergency Departments	949,585	108,071	0.7	0.07
Chest pain, unspecified '786.50'				
All ambulatory settings	11,177,221	1,129,979	0.88	0.08
Physician offices	6,813,018	1,059,080	0.66	0.1
Hospital Outpatient Departments	297,992	62,167	0.31	0.06
Hospital Emergency Departments	4,066,211	307,018	2.99	0.17
Chest pain '786.5'				
All ambulatory settings	15,513,257	1,373,090	1.22	0.1
Physician offices	8,979,784	1,278,831	0.87	0.11
Hospital Outpatient Departments	480,523	97,283	0.50	0.09
Hospital Emergency Departments	6,052,950	404,324	4.45	0.2

Note. Adapted from "Number and Percent of Visits to Different Ambulatory Settings by Patients with Diagnosis of Unspecified Chest Pain," by National Center for Health Statistics /CDC, 2009.
(n) Number of visits
(SE) Standard error of number of visits
(%) Percent of annual visit volume
SE (%) Standard error of percent
*- Estimate does not meet NCHS standards of reliability.
… Inapplicable

Problem Background

The National Hospital Ambulatory Medical Care Survey (1999–2008) reported chest pain as the second most common reason for emergency department visits behind abdominal pain. There were 5 million visits for chest pain between 1999 and 2000; and 5.5 million visits between 2007 and 2008 (Centers for Diseases Control and Prevention, 2010). The annual cost of evaluation of NCCP is estimated to be between $315 million and $1.8 billion (Leise et al., 2010).

Symptoms of chest pain are a major source of concern for both patients and healthcare providers because they can indicate an acute life-threatening event regardless of a history of cardiac disease (Sheps, Creed, & Clouse, 2004). Patients' history and characteristics do not always distinguish between different causes of chest pain. And as a result, many patients seek further medical attention when complaining of chest pain despite previous negative cardiac workups and/or hospitalizations (Fass & Achem, 2011).

Esophageal disorders can also be the etiology of chest pain (Lemme, Moraes-Filho, Domingues, Firman, & Pantoja, 2000). Gastroesophageal reflux disease (GERD) is the main underlying mechanism of NCCP, accounting for up to 60 % of cases (Leise et al., 2010). NCCP can also be caused by esophageal motor dysfunction; and the frequency may be underestimated. Motor disorders are observed in almost 50% of patients with NCCP who ultimately undergo conventional manometry evaluation (Gambitta et al., 1999).

The use of high resolution manometry (HRM) has changed the diagnostic approach to esophageal motility disorders. It is the most specific and sensitive test for diagnosing motor disorders and could be a promising diagnostic procedure in detecting dysmotility disorders in patients with NCCP. The technique uses multiple high-fidelity sensors that capture manometric

data as a spatial continuum without the substantial gaps between pressure sensors typically seen with conventional manometry (Bansal & Kahrilas, 2010). Appendix A highlights the benefits of high resolution manometry compared to conventional manometry.

Despite the increased sensitivity of HRM compared to conventional manometry, the main indications for esophageal manometry remain unchanged. The most frequent indications for esophageal manometry according to the American Gastroenterology Association (AGA) are dysphagia, preoperative assessment of patients who are being considered for anti-reflux surgery, and placement of intraluminal devices (e.g., pH probes) when position is dependent on the relationship to functional landmarks, such as the lower esophageal sphincter (LES) (Pandolfino & Kahrilas, 2005a). At present and since 2004, there is no specific recommendation from the AGA for the use of esophageal manometry in patients with NCCP.

Research Questions

This study's aim is to address two questions:

1. For patients with NCCP who are referred for HRM, what percentage is found to have previously undiagnosed esophageal motility disorders?
2. Are there significant differences in HRM findings in patients with NCCP versus patients who meet current AGA criteria for the use of esophageal manometry?

Purpose of Study

The purpose of this study is to (a) analyze manometric findings obtained with HRM in patients with chest pain in whom cardiac causes were excluded and endoscopic evaluation was unremarkable, (b) assess the importance of method and protocol in establishing a diagnosis of

esophageal dysmotility, and (c) establish a more defined role for esophageal manometry in the NCCP diagnostic protocol.

Definition of Terms

Non-Cardiac Chest Pain (NCCP)

Noncardiac Chest pain is defined as recurrent chest pain that is indistinguishable from ischemic heart pain after a reasonable workup has excluded a cardiac cause (Fass & Achem, 2011).

High Resolution Esophageal Manometry

"High resolution manometry is a new technology used to measure intraluminal pressure activity within the gastrointestinal tract using a series of closely spaced pressure sensors within the esophagus. It uses a series of 36 1-cm-spaced pressure sensors that provides detailed pressure information that reveals the segmental nature of esophageal peristalsis" (Parkman, McCallum, & Rao, 2011, p. 22).

Esophageal Motor Dysfunction

Esophageal motor dysfunction is defined as the impairment of one or more of the mechanisms necessary for normal esophageal function (Greenberger, Blumberg & Burakoff, 2009).

Implications for Practice

Noncardiac chest pain is a common challenge for healthcare providers with respect to diagnostic strategy as well as therapeutic intervention for years (Minocha & Joseph, 1995). The implications of this study on practice include: (a) proper diagnosis of patients with NCCP, (b) increased patient satisfaction and quality of life through appropriate diagnosis and treatment, (c)

decrease patients' anxiety which results from frequent diagnostic uncertainty, (d) increase awareness among primary healthcare providers and cardiologists regarding the importance of HRM in the evaluation of NCCP.

CHAPTER TWO: LITERATURE REVIEW

Noncardiac Chest Pain

The definition of NCCP is complex. In a broad context, NCCP is chest pain that is not related to angina or ischemic heart disease (Fox & Forgas, 2006). NCCP is further defined as recurrent episodes of substernal chest pain or discomfort that remains unexplained after nonesophageal causes such as cardiac, musculoskeletal, pleuritic, or pulmonary pathologies have been excluded (Kachintorn, 2005). NCCP is not a recent pathophysiological phenomenon; it was first recognized in 1860. It was called soldier's heart as it described British soldiers who presented with new onset chest pain during war (Minocha & Joseph, 1995).

Epidemiology

There are limited national and international epidemiological data on NCCP (Fass &Achem, 2011). Internationally, one in four persons has an episode of chest pain annually (Eslick et al., 2005). There is no difference in the prevalence of NCCP between males and females (Kachintorn, 2005). However, females with NCCP tend to seek care more often than men (Fass & Navarro-Rodriguez, 2008). Epidemiological studies have reported a decreased prevalence of NCCP with increasing age. Females under the age of 25 and those between 45 and 55 years of age were found to have the highest prevalence rates (Fass & Dickerman, 2006; Eslick & Fass, 2003).

Data also suggest patients with NCCP are often already actively under the care of a physician, specialist, or other healthcare practitioner. Eslick and Tally (2004) found that 80% of patients who presented to the emergency department with acute chest pain had seen a healthcare provider within 12 months. The most common healthcare providers seen by patients in their

sample were general practitioners (85%), cardiologists (74%), gastroenterologists (30%), pulmonologists (14%), alternative therapists (8%), and psychologists (10%).

In summary, NCCP is a common medical problem in the community that affects both sexes equally. However, females are more likely to present to the emergency department for evaluation of chest pain.

Causes

There are many common causes for NCCP that are not limited to the esophagus. Pulmonary-, musculoskeletal-, infectious-, cardiovascular-, drug-, psychological-, and gastroenterology-related disorders may present as atypical chest pain. Specific examples of these conditions are listed in Table 2. The scope of this exposition will be limited to patients with NCCP who presented to a gastroenterology office to rule out gastroenterology –related disorders after cardiac workup was unremarkable.

Table 2: Common Non cardiac Chest Pain Causes

Musculoskeletal	Gastrointestinal	Pulmonary	Miscellaneous

• Costochondritis
• Fibromyalgia
• Precordial catch syndrome
• Slipping rib syndrome
• Tietze's syndrome
	• Gastric
	• Biliary tree
	• Gallbladder
	• Pancreatic
	• Intra-abdominal masses
	• Esophageal causes:
	  ○ GERD
	  ○ Visceral Hypersensitivity
	  ○ Esophageal dysmotility
		• Pneumonia
		• Pulmonary embolism
		• Lung cancer
		• Sarcoidosis
		• Pneumothorax
		• Pneumomediastinum
		• Pleural effusions
		• Intrathoracic masses
			• Aortic disorders
			• Pericarditis and myocarditis
			• Pulmonary hypertension
			• Herpes zoster
			• Drug-induced pain
			• Sickle cell crises
			• Psychological disorders

Note. Adapted from "Noncardiac Chest Pain: Epidemiology, Natural Course and Pathogenesis," by R. Fass and S. Achem, 2011, *Journal of Neurogastroenterology and Motility*, 17, p. 112.

Functional Anatomy of the Esophagus

The esophagus and its sphincter act in coordination to perform the tasks of transporting swallowed substances to the stomach and prevent the reflux of gastric contents while allowing venting of gaseous gastric contents. Behind this coordination is a complex neuronal system within the esophageal wall and the central nervous system (Bredenoord & Smout, 2008).

The esophagus is a 20-22 cm tube. It is composed of three functional regions: the upper esophageal sphincter (UES), the esophageal body, and the LES. The UES is composed of striated muscle. It is usually closed at rest and opens when a peristaltic pharyngeal contraction approaches to allow bolus passage across the sphincter. The esophageal body is a muscular tube that connects the UES and the LES. It consists of an inner circular muscle layer and outer longitudinal muscle layer. There is a mesenteric plexus between the circular and longitudinal muscle which regulates muscle actions. The enteric nervous system receives input from the central nervous system. The LES consists of a circular smooth muscle thickening at the esophageal gastric (GE) junction. The sphincter relaxes as the bolus enters the upper esophagus and stays relaxed until the peristaltic contraction arrives at the GE junction (Bredenoord & Smout, 2008).

Nature of Noncardiac Chest Pain

The close anatomical relationship between the esophagus and the heart contributes to the similarity in symptoms and the difficulty in distinguishing the origin of chest pain. The esophagus is located posterior to and is separated from the left atrium by the pericardium. Both the heart and the esophagus share the same common path of pain fibers from the sympathetic trunk (Heatley, Rose & Weston, 2005).

Esophageal pain has many patterns. Patients usually describe it as burning, gripping, stabbing, and pressing. In the anterior chest, the pain is usually in the throat or epigastrium and sometimes radiates to the neck, back or upper arms. These symptoms may also apply to cardiac pain (Bennett, 2001). Still, it is widely understood that the characteristic pain of GERD is burning, epigastric, and related to recent food intake, lying down or bending (Bennett, 2001). Pain as a result of esophageal spasms is retrosternal, deep and often labeled as burning, squeezing or aching, usually radiating to the arms, jaw, and back (Heatley, Rose & Weston, 2004).

Many risk factors are associated with the development of coronary diseases, such as smoking, obesity, and diabetes mellitus. Complicating the clinical picture, these risk factors also increase the likelihood of esophageal disorders. Medical treatments designed for angina (e.g., nitroglycerin) often helps to relieve symptoms originating from the esophagus (Heatley, Rose & Weston, 2004).

Pathophysiology

The potential for an esophageal etiology for recurring NCCP was originally hypothesized by William Osler in 1892 (Castell, Talley, & Travis, 2010). The specific mechanisms for esophageal-induced NCCP are poorly understood (Fang & Bjorkman, 2001). However, a few possible mechanisms have been identified and include: irritant stimuli to the esophageal mucosa, mechanical effects on the muscular wall, and visceral hypersensitivity (Castell et al., 2010).

Mucosal stimulation. Chest pain arises from esophageal mucosal irritation by acid exposure. This causes discomfort in most patients. It usually resolves when acid perfusion ceases (Bennett, 2001).

Mechanical changes. Alterations in esophageal motility can be a cause of chest pain. This includes achalasia (absent distal peristalsis or abnormal relaxation of the LES), diffuse esophageal spasm (DES) (simultaneous contractions or intermittent peristalsis), nutcracker esophagus (increased contraction amplitude of over 180 mm Hg with normal peristalsis), hypotensive LES, and ineffective esophageal motility (contractions of low amplitude or failed and non-transmitted) (Bennett, 2001).

Visceral hypersensitivity. Chest pain caused by alterations in visceral receptor sensitivity; the prevalence is higher in patients with anxiety, depression, somatization, and neuroticism (Bennett, 2001).

Non Cardiac Chest Pain Cost

While the economic burden of NCCP has been proposed to be very high, studies evaluating the cost and its impact on the healthcare system are scarce (Fass & Achem, 2011). In one study, the healthcare costs for NCCP were estimated to be more than $315 million annually (Richter, Barish, & Castell, 1986). And a more recent estimate put the cost at $1.8 billion annually (Fang & Bjorkman, 2001). The high costs of NCCP are related to the need for frequent clinic and emergency room visits, hospitalizations, and costly medications often prescribed to NCCP patients. The cost excludes indirect expenses such as lost days of work, productivity and the impact of symptoms on patients' quality of life (Richter et al., 1986).

The cost of NCCP evaluations can be considerable. Thirty percent of coronary angiograms performed in patients with chest pain are normal or have insignificant degrees of obstruction. An estimated 1-1.5 million angiograms are performed annually. The long-term mortality of NCCP patients is low with reported rates of < 1% at 10 years. Still, morbidity

remains high, accounting for the significant healthcare costs in treating these patients (Fang & Bjorkman, 2001).

Non Cardiac Chest Pain Treatment Algorithm

An algorithm outlining an approach in patients with NCCP was published by Fang and Bjorkman (2001) and is presented in Figure 1. While it has not been adopted by the AGA for treating patients with NCCP, it includes the use of esophageal manometry as part of the NCCP workup.

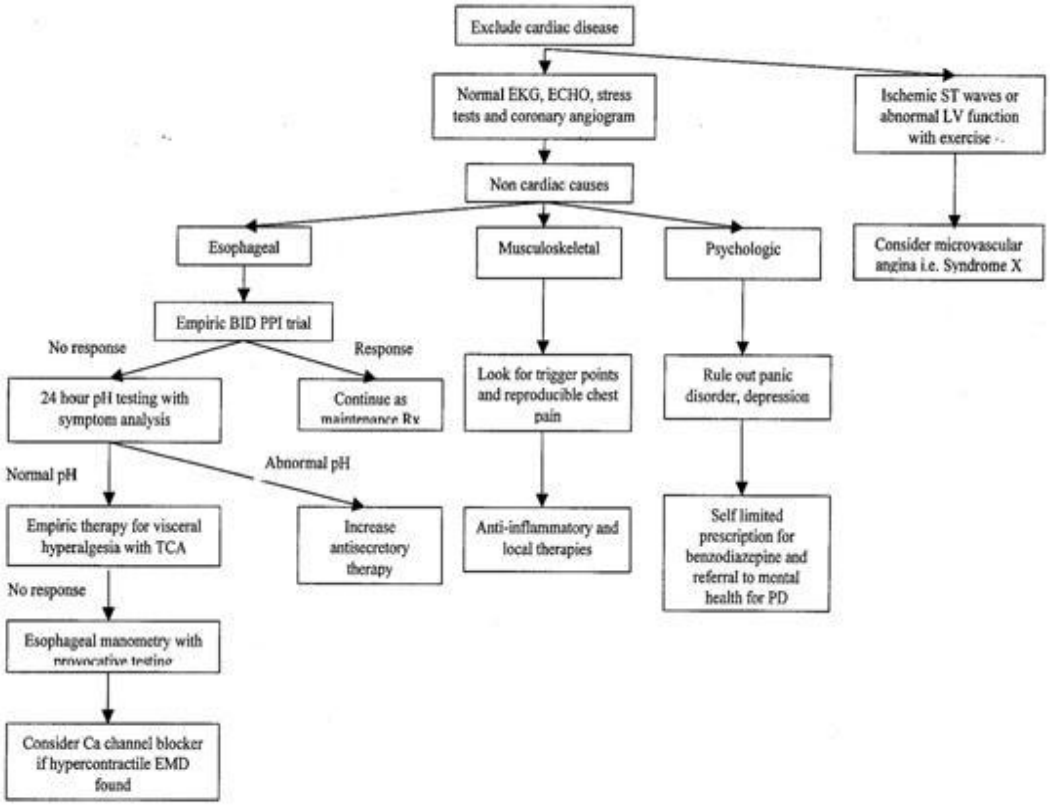

Figure 1: Unexplained cardiac chest pain algorithm. From "A Critical Approach to Noncardiac Chest Pain: Pathophysiology, Diagnosis, and Treatment," by J. Fang, and D. Bjorkman, 2001, The American Journal of Gastroenterology, 96, p. 965. Copyright 2001 by Macmillan Publishers Ltd. Reprinted with permission.

An Overview of High Resolution Manometry

High resolution manometry is the latest development in the recording of esophageal pressure (Bredenoord & Smout, 2008). Conceptually, HRM refers to the use of multiple high-fidelity sensors to capture manometric data as a spatial continuum without the substantial gaps between sensors typical of conventional manometry (Bansal & Kahrilas, 2010). HRM provides more data in comparison to conventional manometry (Park, 2010). It represents a refinement in conventional methodology that provides greater detail by simplifying data interpretation (Hirano & Pandolfino, 2007). It is designed to overcome the limitations of conventional manometric systems (Park, 2010). Esophageal manometry has grown from a restricted technique in specialized centers to a widespread clinical tool; and the number of studies assessing its efficacy are increasing (Bredenoord & Smout, 2007).

History

The first manometric study was performed by Meltzer and Kronecker in 1883; and the first pressure measurement of the esophagus was introduced in the late 1950s (DiMarino, Allen, Lynn, & Zamani, 1998). Since then, there has been a stepwise improvement in the technique. Earlier manometric evaluations were conducted using a pull through technique, where a catheter with a few perfused side holes was used to identify pressure patterns in the esophagus. This technique helped in recognizing a zone of high pressure at the GE junction. In addition, peristalsis of the esophagus could be observed and the amplitude, duration, and velocity of the propulsive contractions could be quantitated. This technique has difficulties mainly on LES relaxation measurement at the GE junction as a result of a single point sensor. During swallowing, the longitudinal muscles of the esophagus contract, resulting in an upward

movement of the LES. This movement causes an issue in recording LES pressures since the sphincter moves away from the point sensor, resulting in a recorded pressure decrease. In 1976, this problem was solved with the addition of a sleeve sensor by Dent. The sleeve is a 6 cm perfused membrane positioned along the distal end of the catheter which records the highest pressure exerted along the membrane. Subsequently, the movement of an unrelaxed LES will not influence pressure registration (Bredenoord & Smout, 2007).

A decade ago, a new advanced HRM, micro-manometry was introduced. The catheter used in this HRM contains smaller lumina that are perfused at very low perfusion rates. This improved catheter enables pressure monitoring with more sensors without overflowing the esophagus with water. Micro-manometry allows the catheter to remain in one position while studying peristalsis at 1-cm intervals in the entire esophagus (Bredenoord & Smout, 2007).

Indication for Esophageal Manometry

Esophageal manometry is considered the gold standard for esophageal motor function assessment after mechanical obstruction and mucosal disease have been excluded by endoscopy and/or barium swallow (Roman, Pandolfino, & Mion, 2009). HRM is clinically useful in the evaluation of patients with nonstructural dysphagia, unexplained and/or NCCP, symptoms suggestive of GERD, and prior to anti-reflux surgery (Katz, Menin, & Gideon, 2008). It is also used to evaluate patients with generalized gastrointestinal tract disease such as scleroderma or chronic idiopathic intestinal pseudo-obstruction (Lembo, Tally, & Travis, 2009)

According to the AGA, the utility of esophageal manometry in clinical practice resides in three areas: (1) to accurately define esophageal motor function, (2) to define abnormal motor

function, and (3) to delineate a treatment plan based on motor abnormalities (Pandolfino, & Kahrilas, 2005b).

Esophageal manometry clinical practice guidelines were developed by the AGA to assist gastroenterologists and other clinicians in the appropriate use of esophageal manometry in patient care. The guidelines were approved by the Clinical Practice Committee on October 2, 2004, and by the AGA Governing Board on November 7, 2004 (Pandolfino, & Kahrilas, 2005a). These guidelines are an update from previous recommendations published in 1994 and represent the results of meticulous research into areas of controversy from the previous policy statement. These recommendations take into account new technologies and techniques that may improve and complement manometric diagnosis and are listed in Table 3 (Pandolfino, & Kahrilas, 2005a).

Table 3: Summary of the Recommendations for the Clinical Use of Esophageal Manometry

Indication	Recommendations
Indicated	1. Manometry is indicated to establish the diagnosis of dysphagia in patients in which a mechanical obstruction cannot be found and the diagnosis of achalasia is suspected. 2. Manometric techniques are indicated for placement of intraluminal devices (e.g., pH probes) when its positioning is dependent on the relationship to functional landmarks, such as the LES. 3. Manometry is indicated for the preoperative assessment of patients who are undergoing anti-reflux surgery.
Possibly indicated	1. Manometry is possibly indicated for the preoperative assessment of peristaltic function in patients undergoing anti-reflux surgery. 2. Manometry is possibly indicated to assess symptoms of dysphagia in patients who have undergone either anti-reflux surgery or treatment for achalasia.
Not indicated	1. Manometry is not indicated for making or confirming a suspected diagnosis of GERD. 2. Manometry should not be routinely used as the initial test for chest pain or other esophageal symptoms because of the low specificity of the findings and the low likelihood of detecting a clinically significant motility disorder.

Note. From "American Gastroenterological Association medical position statement: Clinical use of esophageal manometry," by J. Pandolfino and P. Kahrilas, 2005, *Gastroenterology*, 128, p. 207. Copyright 2005 by Elsevier. Adapted with permission.

The AGA recommendations for the clinical use of esophageal manometry do not include assessment of patients with NCCP. This issue has been considered as the most controversial application of esophageal manometry (Pandolfino, & Kahrilas, 2005b). Low specificity of the esophageal manometry findings and the low likelihood of detecting a clinically significant motility disorder have limited the clinical use of esophageal manometry in patients with NCCP

(Pandolfino, & Kahrilas, 2005b). And while it remains absent from the guidelines, HRM has been used successfully to detect motility diseases in patients with NCCP. For example, Mehendiratta, DiMarino, and Cohen (2009) in their study showed a high clinical utility of esophageal manometry in patients with dysphagia and/or NCCP. Figure 2 lists examples of abnormal findings that can be evaluated by esophageal manometry.

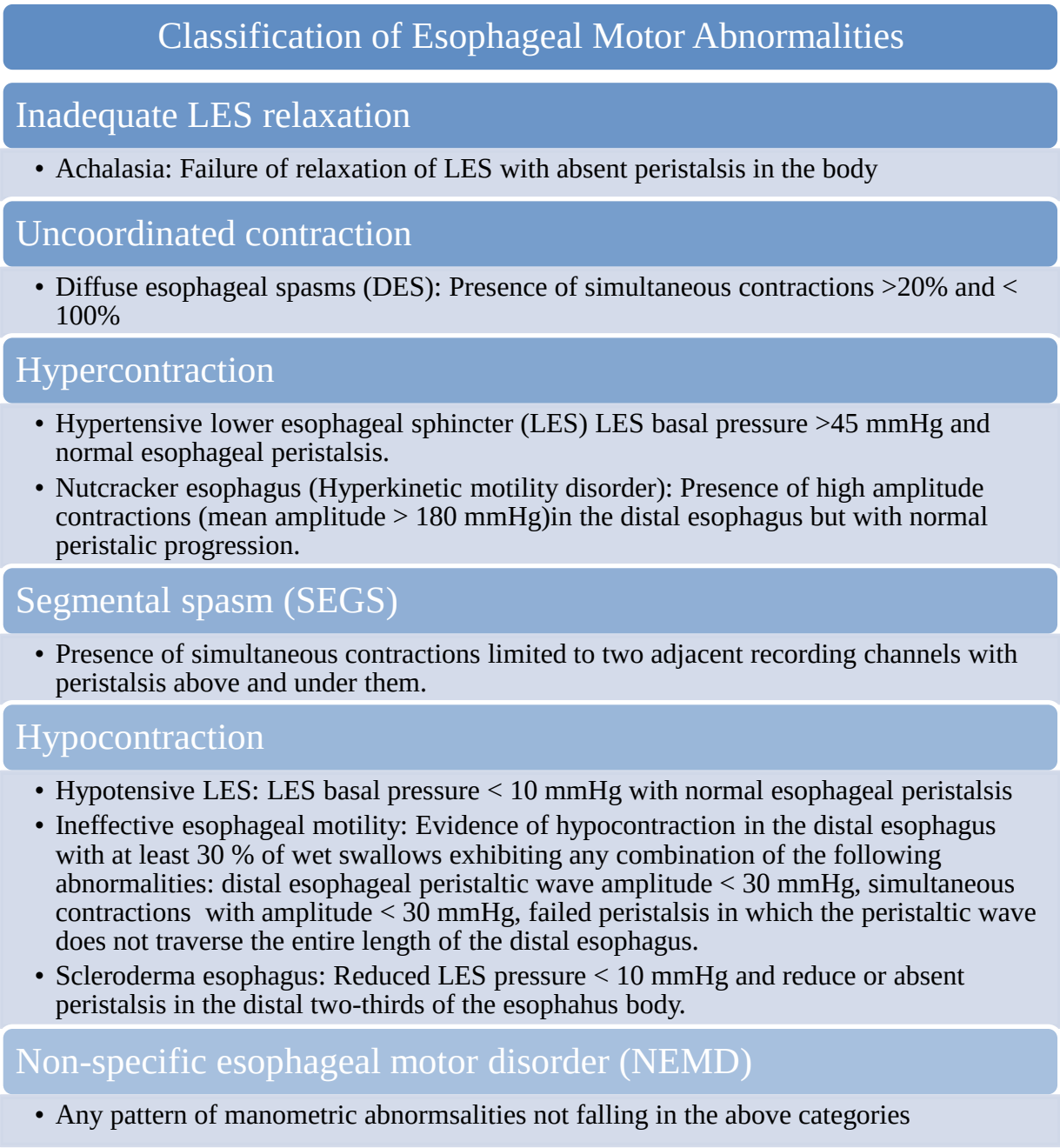

Figure 2. Esophageal Motor Abnormalities. From "Manometric Findings of Esophageal Motor Disorders in 240 Brazilian Patients with Non-cardiac Chest Pain," by E. M. Lemme, J. P. Moraes-Filho, G. Domingues, C. G. Firman, and J. A. Pantoja , 2000, *Diseases of the Esophagus*, 13, p. 118. Copyright 2000 by John Wiley and Sons. Adapted with permission. From "Clinical Utility of Selective Esophageal Manometry in a Tertiary Care Settings," by V. Mehendiratta, A. DiMarino, and S. Cohen, 2009, *Digestive Diseases and Sciences*, 54, p. 1482. Copyright 2009 by Springer Science and Business Media. Adapted with permission.

The State of Science Regarding the Use of Esophageal Manometry in Patients with Non Cardiac Chest Pain

Approximately 30% of patients undergoing cardiac workup have normal findings (Arora & Katzka, 2011). One-third of patients with NCCP and non-GERD-related chest pain have various esophageal motility abnormalities (Fass, 2008).

Esophageal manometry combined with acid perfusion has been found to be a safe and reliable technique for the diagnosis of patients with NCCP since 1991. Pathologists discovered abnormal findings in these NCCPs, including high-amplitude peristalsis and DES. Of the 275 patients, 90 patients had a positive response on combined esophageal manometry and acid perfusion studies. The investigators recommended using esophageal manometry with acid perfusion studies as a primary method for distinguishing esophageal pain from cardiac pain (Crozier, Glick, Gibb, Ellis, & Veerman, 1991).

Similar findings were also found by Lemme et al. (2000). Esophageal manometry showed abnormalities in 151 (63%) patients. The most frequent abnormal findings were non-specific esophageal motor disorders (n = 60), and hypotensive LES (n = 54). Fifteen patients had nutcracker esophagus, 4 DES, 11 segmental spasm, 6 achalasia, and 1 hypertensive LES. The final conclusion of the study confirmed the usefulness of esophageal manometry in the assessment of patients with NCCP. These authors also recommended patients with NCCP to be referred for manometric evaluation.

Two most recent studies showed the role of esophageal manometry in patients with NCCP. Dekel et al. (2003) assessed esophageal manometry in patients with NCCP and dysphagia and discovered many had hypotensive LES in the NCCP group of the study, ineffective peristalsis in the dysphagia study group, and achalasia in patients with combined

symptoms of NCCP and dysphagia. Lacima, Grande, Pera, Francino, and Ros (2003) found that ambulatory manometry had a small but perhaps important impact on the diagnosis of patient with NCCP compared to standard esophageal testing.

In summary, not many studies have been dedicated to the evaluation of patients with NCCP and esophageal motor dysfunction. However, while the studies mentioned above were all supportive for the use of esophageal manometry in patients with NCCP, they assessed the role of conventional manometry rather than HRM.

CHAPTER THREE: METHODOLOGY

The focus of this study is to determine if HRM should play a more significant role in the evaluation of patients with NCCP. The aim of this study is to (a) analyze manometric findings obtained with HRM in patients with chest pain in whom cardiac causes were excluded and endoscopic evaluation was unremarkable, (b) assess the importance of method and protocol in establishing a diagnosis of esophageal dysmotility, and (c) establish a more defined role for esophageal manometry in the NCCP diagnostic protocol.

Setting

The setting of this study was a gastroenterology office located in Maitland, Florida. It is a private office including four board-certified gastroenterologists and one board-certified adult nurse practitioner (ANP-BC). Esophageal manometry is one of multiple procedures performed at this office and is usually done 5 days per week. The patients for esophageal manometry are usually referred by gastroenterologists and surgeons. The most frequent indications for referrals are dysphagia, intractable GERD, and preoperative assessment prior to anti-reflux surgery. These patients are diverse in their race, gender, ethnicity, and socioeconomic status. They represent a mix of health insurance coverage including private insurance, Orange County, Medicaid, Medicare, self-pay, and others.

Design

This is a descriptive, cross sectional study that uses a two by two design.

Sample

The sample included 219 patients who underwent HRM from January 2009 to January 2012 and met the study's inclusion criteria. The sample was grouped into: (a) NCCP group (*n* =

52) which included patients with chest pain and had negative cardiac workups; and (b) AGA group (n = 168) which included patients who met the AGA criteria for esophageal manometry. Both groups had negative endoscopic evaluation of any esophageal stricture. The inclusion criteria included: (a) All patients must have had a negative endoscopic and/or barium swallow evaluation for anatomical abnormalities, (b) All patients must have had an extensive cardiac workup for chest pain which was non-diagnostic, and (c) patients must be 18 years of age or above. Any patient who did not meet the above criteria was excluded. Data were collected through retrospective chart review; therefore there was no contact with patients.

Procedure

Health records that met inclusion criteria were electronically accessed and reviewed. Data were input into Excel spreadsheet and then transferred into the statistical analysis system (SAS) version 9.2.

Study Variables

The demographic variables included age, gender, ethnicity/race and health insurance. Table 4 specifies data collected for each variable.

Table 4: Demographic Data

Gender	Age	Ethnicity/Race	Insurance
• Male • Female	• 18-29 • 30-39 • 40-49 • 50-59 • 60-69 • 70-79 • 80-89	• White • African American • Hispanic • Asian	• Yes • No

The dependent variable is the results/diagnosis found during the HRM procedure. The independent variable is the use of HRM. Abnormal results included the diagnosis of any of the following: Achalasia, nutcracker esophagus, hypotensive or hypertensive LES, DES, and nonspecific findings.

Data Analysis

Descriptive statistics; including mean, standard deviation, range, frequency and percentage, were calculated to describe the study sample (gender, age and ethnicity/race) and summarize the results of the HRM procedures (achalasia, nutcracker esophagus, hypotensive LES, hypertensive LES, DES, nonspecific findings, normal results in the three categories of NCCP, mixed symptoms and indication of esophageal manometry group). Chi square was used to address the research questions. SAS version 9.2 was used to analyze the data.

Ethical Considerations

This study did not require direct interaction with patients. Patients' names were not recorded from collected data. Instead, coded numbers were used to identify records within the database. Therefore the potential for identification of patients' names was eliminated. Consent was not needed from patients. All medical records were kept on a computer housed in a locked office. The study was approved by the Institutional Review Board of the University of Central Florida.

CHAPTER FOUR: FINDINGS

Introduction

The purpose of this study was to (a) analyze manometric findings obtained with HRM in patients with chest pain in whom cardiac causes were excluded and endoscopic evaluation was unremarkable, (b) assess the importance of method and protocol in establishing a diagnosis of esophageal dysmotility, and (c) establish a more defined role for esophageal manometry in the NCCP diagnostic protocol. The dependent variable is the results/diagnosis of the HRM. The independent variable is the use of HRM. The demographic variables included age, gender, ethnicity/race and health insurance status.

Frequency measures were used to answer the first research question: (1) For patients with NCCP who are referred for HRM, what percentage is found to have previously undiagnosed esophageal motility disorders? Chi-square with Fisher's exact test was used to answer question number two: (2) Are there significant differences in HRM findings in patients with NCCP versus patients who meet current AGA criteria for the use of esophageal manometry? All data analyses were performed with the use of SAS version 9.2.

Demographics

Over 3 years (January 2009 to January 2012), a total of two hundred nineteen patients were studied by HRM at the Center for Advanced Gastroenterology office in Maitland, Florida. One hundred sixty eight (77%) patients underwent HRM and fell under the AGA recommendations for esophageal manometry. Fifty one (23%) patients with negative cardiac evaluation underwent HRM to evaluate their chest pain. Before manometry, all patients underwent endoscopy and obstructive lesions were excluded.

Complete demographic data for the sample are shown in Table 5. The majority of participants were female (74%), white (61%) and insured (99%) with a mean age of 57 ± 15.

Table 5: Demographic Data: Frequency and Percent

	Variable	Frequency (n)	Percent (%)
Gender	Female	163	74
	Male	56	26
Age	18-29	8	4
	30-39	20	9
	40-49	35	16
	50-59	54	25
	60-69	46	21
	70-79	41	19
	80-89	15	7
Ethnicity/Race	African American	46	21
	Asian	6	3
	Hispanic	33	15
	Indian	1	0.5
	White	133	61
Insurance	No	3	1
	Yes	216	99

Note. The percentage was rounded to the nearest number
Percentages do not sum to a 100 due to rounding

Figures 3, 4 and 5 are graphical representations of the sample's demographic data: gender, age, and ethnicity/race.

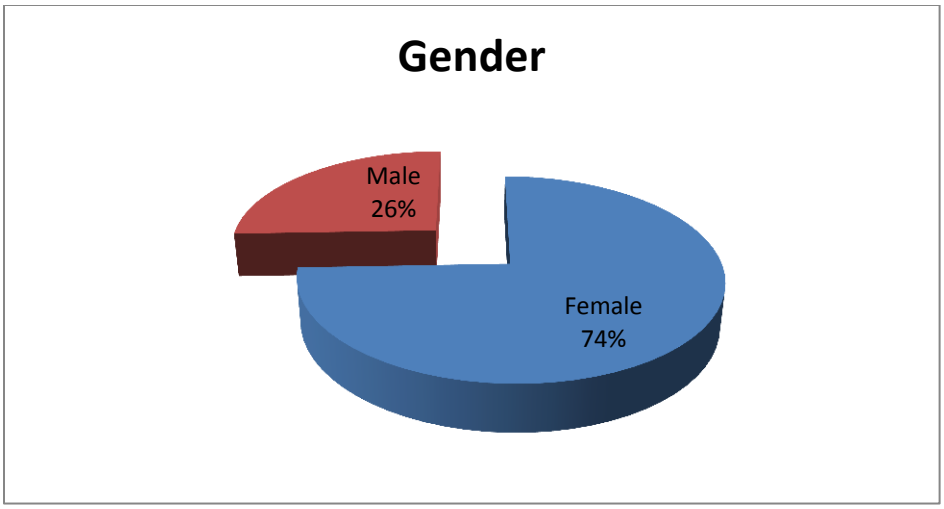

Figure 3. Gender

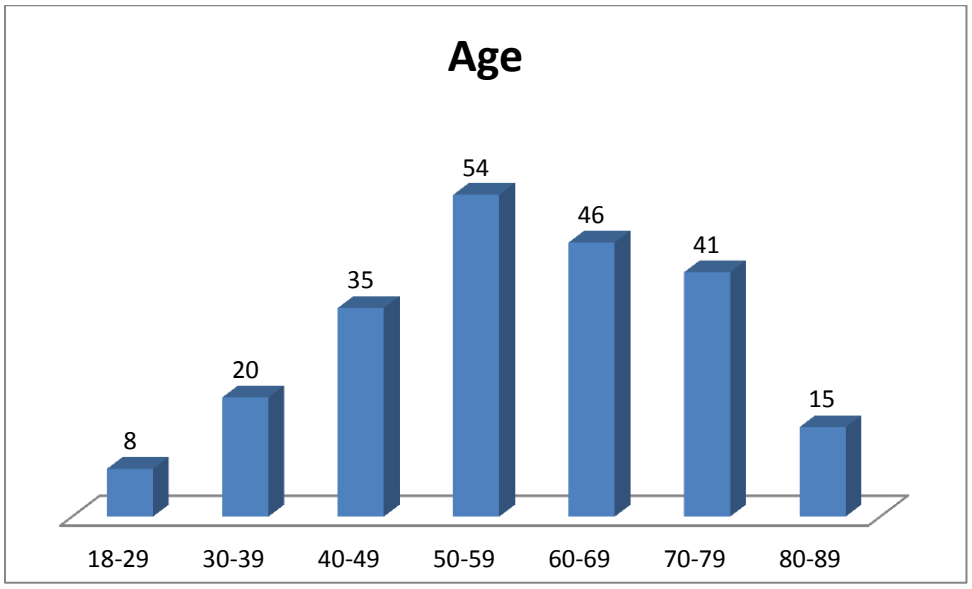

Figure 4. Age

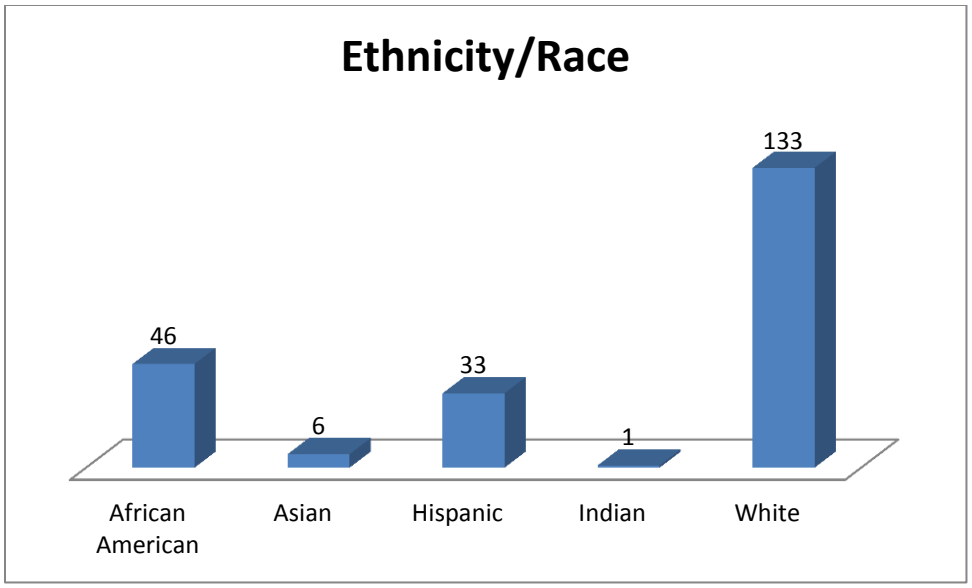

Figure 5. Ethnicity/Race

Research Questions

Question one: For patients with NCCP who are referred for HRM, what percentage is found to have previously undiagnosed esophageal motility disorders?

The results of the HRM were divided into nine categories (achalasia, DES, hypertensive LES, hypotensive LES, ineffective esophageal motility, nonspecific findings, nutcracker, scleroderma, and normal). DES was the most prevalent abnormal finding in the NCCP group. Esophageal manometry was abnormal in 67% of NCCP patients. Abnormalities included: achalasia 6%, nutcracker esophagus 6%, DES 47%, hypotensive LES 20%, hypertensive LES 3%, scleroderma 3%, ineffective esophageal spasms 9%, and nonspecific findings 6%. Figures 6 and 7 provide graphical representation of HRM results in the NCCP group.

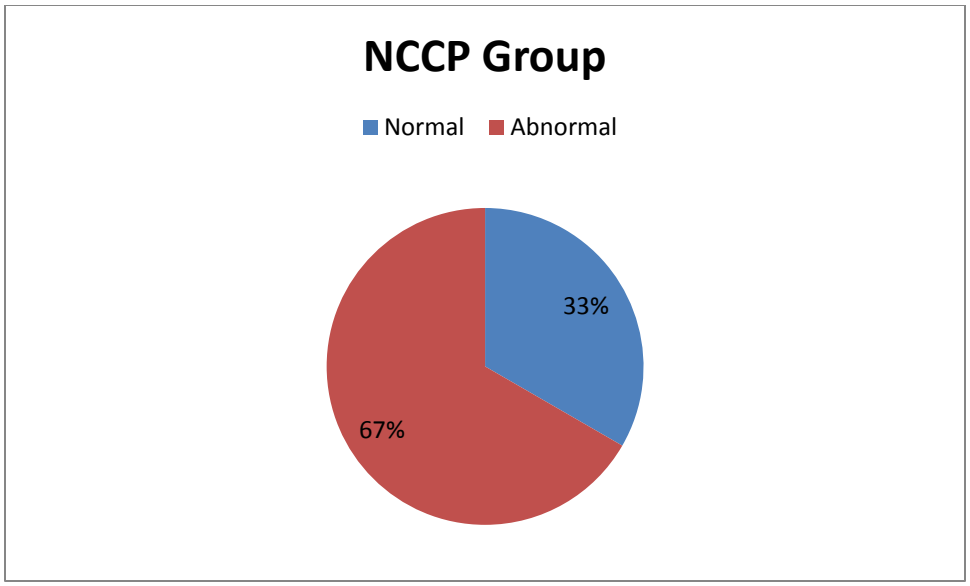

Figure 6: The Percentage of Normal and Abnormal HRM Findings in NCCP Group

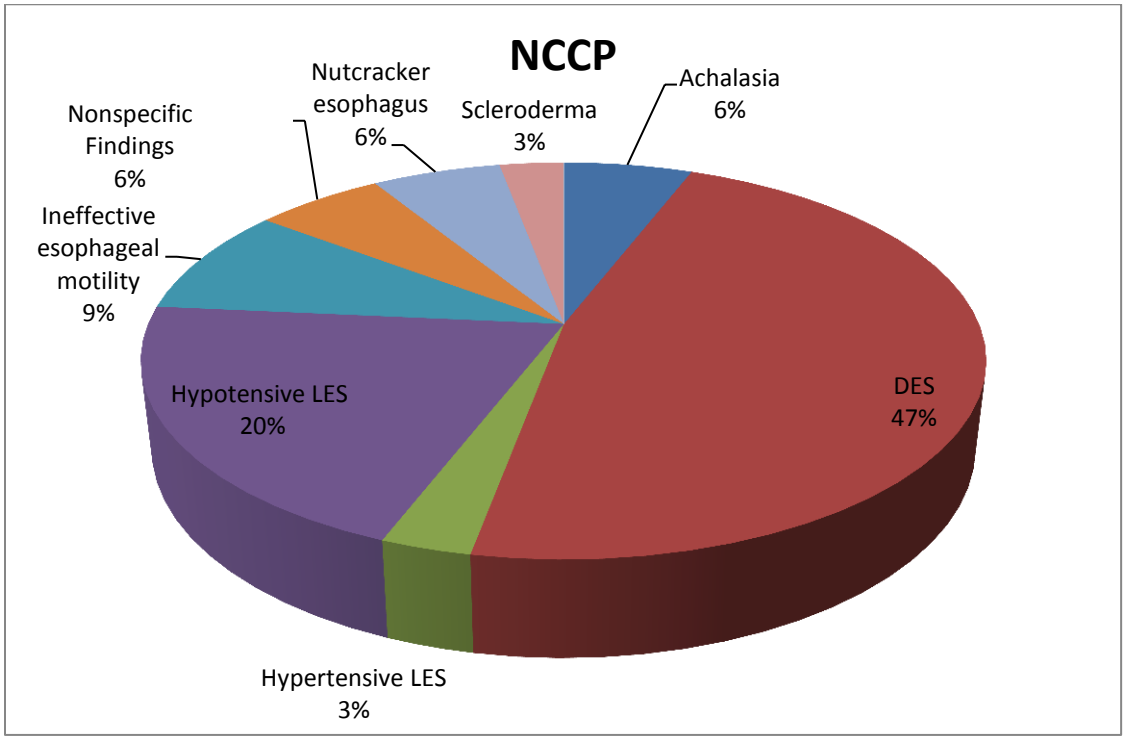

Figure 7: The Percentage of Abnormal HRM Findings in NCCP Group

Question two: Are there significant differences in HRM findings in patients with NCCP versus patients who meet current AGA criteria for the use of esophageal manometry?

Results of HRM in the AGA group

Manometric abnormality was identified in 69% of patients in the AGA group. Abnormalities included: achalasia 16%, nutcracker esophagus 13%, DES 27%, hypotensive LES 15%, hypertensive LES 4%, scleroderma 3%, ineffective esophageal spasms 6%, and nonspecific findings 16%. Figures 8 and 9 provide graphical representations of HRM results in the AGA group.

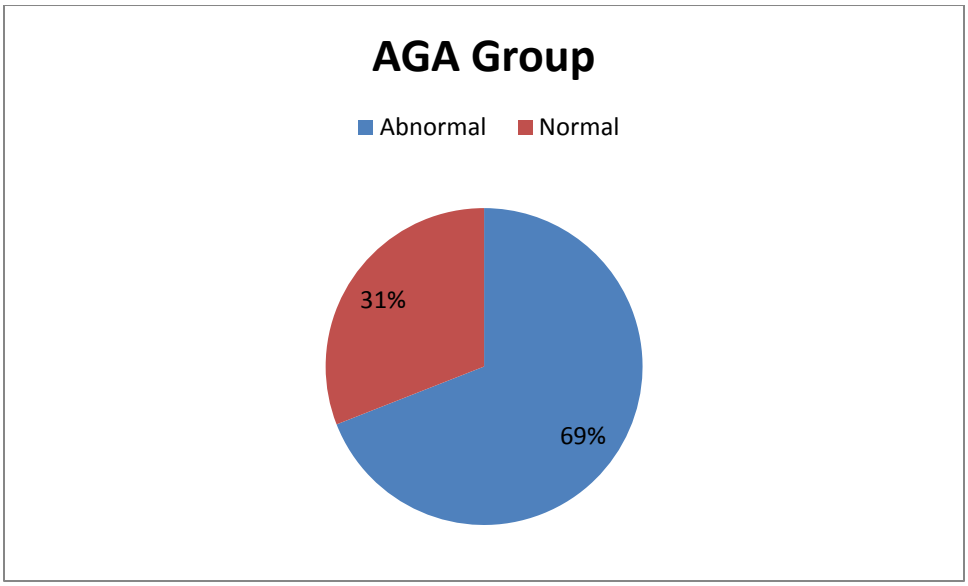

Figure 8: The Percentage of Normal and Abnormal HRM Findings in AGA Group

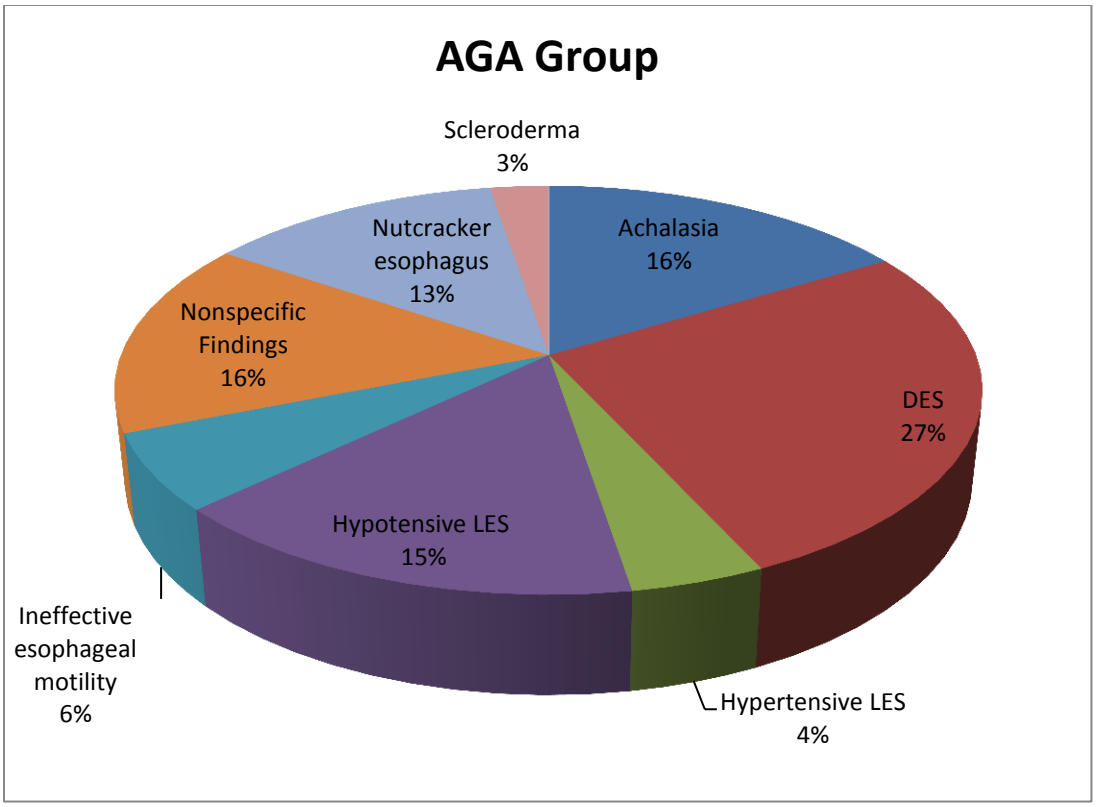

Figure 9: The Percentage of Abnormal HRM Findings in AGA Group

Table 6 compares the findings of HRM in both NCCP group and AGA group. It provides data about the frequency and percent of each diagnosis / finding on HRM.

Table 6: Results of High Esophageal Manometry

Diagnosis / Finding		AGA Group	NCCP Group	Total
Achalasia	(n)	19	2	21
	(%)	9	1	10
DES	(n)	31	16	47
	(%)	14	7	21
Hypertensive LES	(n)	5	1	6
	(%)	2	0.5	3
Hypotensive LES	(n)	18	7	25
	(%)	8	3	11
Ineffective esophageal motility	(n)	7	3	10
	(%)	3	1	5
Nonspecific Findings	(n)	18	2	20
	(%)	8	1	9
Nutcracker esophagus	(n)	15	2	17
	(%)	7	1	8
Scleroderma	(n)	3	1	4
	(%)	1	0	2
Normal	(n)	52	17	69
	(%)	24	8	32
Total		168	51	219
Total Percentage		77	23	100

Note. The percentage was rounded to the nearest number
Percentages do not sum to a 100 due to rounding
(n) Frequency
(%) Percentage

Figure 10 provides a graphical comparison of the HRM results between NCCP group and AGA group.

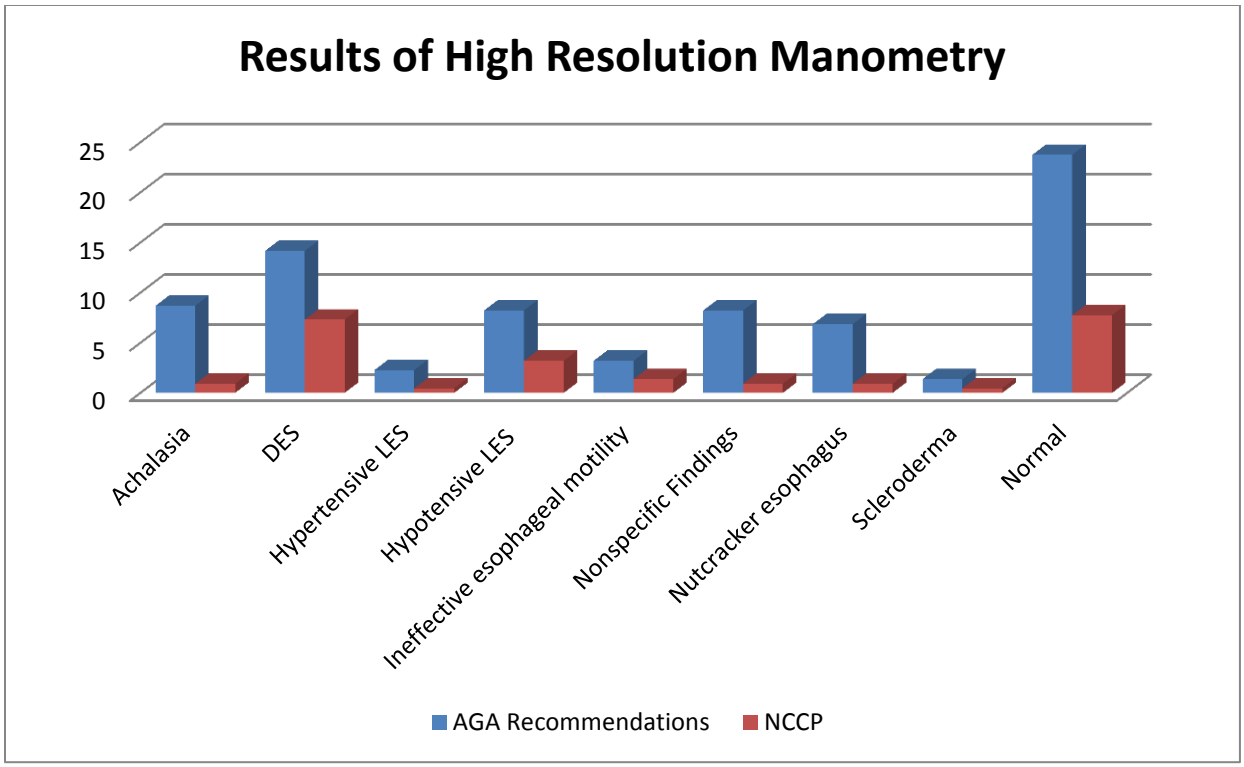

Figure 10: Results of High Resolution Manometry

The results of the HRM were grouped into two categories: (1) Abnormal findings (achalasia, DES, hypertensive LES, hypotensive LES, ineffective esophageal motility, nonspecific findings, nutcracker, and scleroderma), and (2) normal findings. In the AGA group, 116 patients (69%) had abnormal findings compared to 52 patients (31%) with normal study. In the NCCP group, 34 patients (67%) had abnormal findings compared to 17 patients (33%) who had normal study. Table 7 summarizes these findings.

Table 7: Normal and Abnormal results of HRM in NCCP Group and AGA Group

		AGA	NCCP	Total
Abnormal	Frequency	116	34	150
	Percent	53	15	68
Normal	Frequency	52	17	69
	Percent	24	8	32
Total		168	51	219
Total Percent		77	23	100

Note. The percentage was rounded to the nearest number

To compare normal and abnormal HRM findings between the NCCP group and AGA group, Chi-Square analysis was performed. The results were not statistically significant (p = 0.10). In addition, the association between each diagnosis found on HRM (achalasia, DES, hypertensive LES, hypotensive LES, ineffective esophageal motility, nonspecific findings, nutcracker esophagus, scleroderma and normal results) between the two groups were individually tested by Chi-Square. Furthermore, the Fisher's Exact Test was used to assess categories with less than 5. Table 8 illustrates the results of both Chi-Square and Fisher's Exact test results for each category. Diffuse esophageal spasms was the only category that was statistically significant (p = 0.05).

Table 8: Chi-Square and Fisher's Exact Test Results

	Fisher's Exact Test	Chi-Square
Achalasia	0.17	
DES		0.05
Hypertensive LES	0.17	
Hypotensive LES		0.55
Ineffective esophageal motility	0.70	
Nonspecific Findings	0.17	
Nutcracker esophagus	0.37	
Scleroderma	1.00	
Normal		0.75

CHAPTER FIVE: DISCUSSION

Detecting an esophageal motor disease allows healthcare providers to assure patients of the benign nature of their condition and provide appropriate treatment. It can also help prevent excessive hospital and physician visits as well as the costly and potentially risky testing which often results.

The first aim of this study was to analyze manometric findings obtained with HRM in patients with chest pain in whom cardiac causes were excluded and endoscopic evaluation was unremarkable.

The findings of this study suggest HRM could play a role in the diagnostic workup in patients with NCCP. Findings in 51 patients with NCCP were compared with findings in 168 patients who met AGA criteria for esophageal manometry. Structural causes were carefully excluded by reviewing endoscopy results from each patient. Esophageal manometry was abnormal in 67% of NCCP patients. Abnormalities included: achalasia 6%, nutcracker esophagus 6%, DES 47%, hypotensive LES 20%, hypertensive LES 3%, scleroderma 3%, ineffective esophageal spasms 9%, and nonspecific findings 6%.

Lemme et al. (2000) showed the majority of patients in their study had nonspecific motility disorders (25%) and hypotensive LES (16%). Katz, Dalton, Richter, Wu, and Castell (1987) found nutcracker as the most common abnormality (48%) followed by nonspecific motor disorder (36%). This study showed the majority of patients to have DES (47%), followed by hypotensive LES (20%). This finding is not consistent with the findings from previous literature. A possible explanation is that this study used HRM, which is more sensitive and specific for diagnosing motor disorders compared to these studies, which used conventional manometry. In

addition, the high percentage of nonspecific findings on previous studies could be a misdiagnosis of DES. This is because HRM is more likely to detect DES or other esophageal motor dysfunction compared to conventional manometry.

The second aim of the study was to assess the importance of method and protocol in establishing a diagnosis of esophageal dysmotility.

Esophageal manometry continues to be of high clinical utility in management of patients with dysphagia after exclusion of mechanical causes. As a result, the main indication for esophageal manometry according to the AGA is dysphagia. However, this study found esophageal manometry to be useful and suggested that perhaps it should play a more prominent role in the evaluation of patients with NCCP. Patients in both groups (AGA and NCCP) had manometric findings that were similar independent of the indication of the esophageal manometry.

The third aim of the study was to establish a more defined role for esophageal manometry in the NCCP diagnostic protocol.

Evaluation of chest pain is the most controversial application of esophageal manometry (Mehendiratta et al., 2008). The literature review that was published by the AGA mentioned that "most patients with chest pain are found to have nonspecific disorders such as those associated with exaggerated contractions in the esophageal body (nutcracker esophagus, hypertensive LES) or those associated with hypotensive LES" (Pandolfino & Kahrilas, 2005 b, p. 219). Therefore, AGA guidelines do not recommend the use of esophageal manometry for initial evaluation of chest pain (even after cardiac and endoscopic workup) as a result of "low specificity of the findings and the low likelihood of detecting a clinically significant motility disorder" (Pandolfino

& Kahrilas, 2005 b, p. 219). Their argument is based on prior studies that reported low incidence of motility disorders (e.g. DES) in patients with NCCP.

Dalton, Castell, Hewson, Wu, & Richter (1991) found that DES is an uncommon motility disorder that is found in less than 5% of patients with chest pain. Consequently, the recommendation was to ignore this diagnosis and to focus on other causes for unexplained chest pain. American Gastroenterological Association recommendations for esophageal manometry were based on studies conducted over 20 years ago that employed "conventional" and "pull through" procedures which are less sensitive than HRM. However, this study provided a cross-section of patients with NCCP. Diffuse esophageal spasms was the most common manometric abnormality seen in 16 (47 %) patients. This could be explained by the use of HRM which is more specific and sensitive for diagnosing motor disorders of the esophagus as compared to conventional manometry. Based on the results of this study, the AGA might need to reassess their recommendation for the use of high resolution manometry.

Findings of this study suggest esophageal manometry could play a more pivotal role in the evaluation of NCCP. Esophageal manometry was made a part of the NCCP workup algorithm and its use would be optimized if healthcare providers were educated on the data supporting it as a diagnostic tool.

Chest pain is an ongoing problem and will continue to be an elusive issue if proper diagnosis is not made for NCCP patients. Many have been seeking medical help as a result of chest pain with repeated cardiac workup and recurrent admission to hospitals. The underuse of HRM has clearly led some patients to remain undiagnosed and thus, suffer needlessly. In turn, this places a significant burden on an already financially strained healthcare system. This study

demonstrates that a brief 30 minute, minimally invasive, and affordable ($200-300) study could provide a diagnosis for many patients who continue to suffer the stress of physical pain and diagnosis uncertainty. One cannot quantify the possibly improved quality of live and peace of mind associated with such a diagnosis and the assurance of a benign course.

Study Strengths

This is potentially the first study to use HRM to look at the percentage of normal and abnormal findings in patients with NCCP. It is also the first to evaluate the differences in HRM findings in patients with NCCP versus those with an AGA indication for the clinical use of esophageal manometry. In addition, all previous studies reviewed assessed conventional manometry. Moreover, most of the studies that were included in the literature review were conducted outside the United States while this one was domestic.

Limitations

The limitation of the study relates to the issues that result with any retrospective chart review; data collected are limited to the information on medical charts and electronic medical records. Another limitation of the study is the sample size. The sample is limited to only patients from Central Florida and from one clinical practice. In addition, most of the NCCP patients were females. However, this finding seems to be compatible with the results from previous studies. These limitations could threaten the generalizability of the findings from the study.

Future Research

The present study provides a basis for further research studies. This study could be replicated in the future using data from multiple centers across the country, which would allow a bigger sample size and more generalizability. In addition, a new study to follow patients after

diagnosis and treatment based on HRM is recommended to evaluate the impact of this procedure in patients' perception of chest pain, recurrence of emergency department visits, hospital admissions, and healthcare providers' office visits would be essential.

Conclusion

The proportion of patients suffering from chest pain in the United States is high. Nearly, all patients with NCCP experience a decreased functionality and quality of life regardless of the cause of the pain, partly from fear of myocardial infarction. There are many causes of chest pain and it is difficult to identify the cause based simply on patients' descriptions and described characteristics of pain (Lenfant, 2010).

In summary, this study is the first to evaluate the use of HRM in patients with NCCP. Based on the results of the present data, the usefulness of HRM in assessing patients with NCCP is strengthened. As a result, patients with NCCP might benefit from HRM studies. In addition, the AGA might need to reassess their criteria for the use of esophageal manometry as a tool in the evaluation of NCCP.

APPENDIX A: BENEFITS OF HIGH RESOLUTION MANOMETRY COMPARED TO CONVENTIONAL MANOMETRY

Benefits of high resolution manometry compared to conventional manometry

Conventional manometry	High-resolution manometry
• Need to move catheter for LES in most systems	• Catheter stays in one position
• Water-perfused systems are multicomponent and cumbersome	• Solid state and direct interface with stand-alone system
• Low fidelity	• High fidelity
• Waveforms only	• Color contour
• LES measurements complex: some use sleeves, others need station pull-through technique	• No need for pull-through technique, and if desired can create an electronic sleeve for LES determination
• Hard to find hiatal hernias	• Hiatal hernias are immediately visible
• Water-perfused catheters are stiff and more uncomfortable	• Soft and comfortable
• Multiple maneuvers mean a longer test duration	• Procedure is quicker since no position changes are needed
• Large gaps between pressure channels (most are 5 cm apart); may miss findings	• Array of 36 channels straddle the entire esophagus; sees the entire organ

Note. From *Color Atlas of High Resolution Manometry* (p. 12), by J. Conklin, M. Pimentel and E. Soffer, 2009, New York: Springer . Copyright 2009 by Springer. Reprinted with permission.

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