Cardiolinguistics Research Study Protocol

1.0 Introduction

While coronary artery disease (CAD) is the leading cause of morbidity and mortality among women, accounting for over one third of total deaths,[1] with a higher worldwide prevalence of angina among women compared to men,[2] a perception that 'CAD is a man's disease' prevails.[3-5]

Not surprisingly, this popular misperception and mal-alignment of actual risk has had negative implications to women as CAD is under-appreciated, under-recognized, under-diagnosed and under-treated among women, receiving less medical therapy and fewer invasive procedures compared to men.[6-13] This difference in the care of women is often interpreted as the "sex/gender bias". And while this bias has been confused by several notable factors, such as differences in CAD incidence rates [5,14,15] and distribution of risk factors according to age,[16] the pervasive nature of this perception has been documented among physicians[17,18] and patients alike.[19-21]

The reasons for this sex/gender bias are likely multifactorial, however an incontrovertible and important factor in the perpetuated sex/gender bias is the perceived differences in symptomology. Early landmark studies characterized heart disease presentation in women as "uncomplicated" [22-25] and labelled as "atypical". However the term "atypical angina" itself, which has become commonly associated with describing symptoms common in women, has no clear definition, even among guidelines.[26,27] This lack of clarity and erroneous assumptions in the early construct of angina may in part explain the sex/gender bias observed affecting the subsequent cardiac care of women. A recent study by Kreatsoulas et al[28] found that when symptoms are mapped along a gender continuum, angina symptoms are remarkably similar among individuals with obstructive CAD and differ principally in the expression of language used to describe their symptoms. The choice of terms used to describe symptoms were found to be a function of gendered language rather than a biological sex difference, as there were no differences found between the sexes in the localization of pain or in associated symptoms among patients with CAD. These findings debunk the myth of "atypical symptoms" and suggest that many of the difference can be attributed to language. However, this too may be overly simplistic; to our knowledge, symptomology studies to date have only captured patient descriptions and not the conversation exchange between physician and patient, which likely also contains important, nuanced information. Prior studies have shown that there is physician variability in history taking in the questions they ask patients that may be influenced by cultural bias[18,29] or by preconceived risk perception.[17,18]

2.0 Hypothesis

To our knowledge, natural language processing (NLP) technology has not been previously used in a clinical setting to analyse differences in the expression of symptoms, and we hypothesize that this novel and advanced technology can act as a sensitive tool able to capture gendered language nuances in the symptomatic expression of cardiac symptoms. We hypothesize that the symptomatic expression of pain will differ in women compared to men

and that NLP technology will substantiate and expand on previous study findings. Further, we expect to capture an interesting interplay of language nuances that may vary according to combinations of patient-physician genders and lastly, we hope to predict obstructive coronary artery disease when cardiac symptoms are analyzed by NLP technology.

3.0 Study Objectives

1) Characterize pain symptoms most commonly experienced in women and men with suspected CAD (inadvertently quantifying how situated gender is in symptoms),
2) Assess the association of symptoms in men and women with their respective angiographic outcomes,
3) Determine speech patterns and conversation content categories of angina symptoms between physicians and patients referred for coronary angiography, clustered by gender and age.
4) Develop machine learning models (probabilistic generative model) to determine symptom expression patterns or a dictionary of symptom expression according to gender that is predictive of coronary artery disease.

4.0 Methods

4.1 Brief overview of study design

Once patients and physicians agree to participate in the study and provide written informed consent, a one-page demographic form and an audio-recorder will be included with the patient's chart. When the physician begins to consult with the patient about their clinical history the physician will be required to turn on the audio-recorder to capture the verbal exchange between physician and patient. There is no intervention for the patient. The patient will receive the standard of care. The angiographic results will be obtained as they become available.

4.2 Selection of Patients

4.2.1 Study Site

This study is a multi-centre study, where all patients must be referred for coronary angiography. Three hospitals with catheterization laboratories will be approached for participation in this study, including Brigham Women's Hospital, Boston, MA, Hamilton General Hospital, Hamilton, ON and St. Michael's Hospital, Toronto, ON. Eligible patients for this study will be approached in the cardiology clinic/ pre-catheterization area in the participating hospitals as they are waiting their coronary angiography procedure. Analysis of the data gathered will be done at the MIT Media Lab and Harvard School of Public Health.

4.2.2 Inclusion Criteria for Patients

- Patients considered eligible for this study are those referred for coronary angiography for a primary diagnosis of suspected CAD and/or a primary diagnosis for angina/cardiac

ischemia. This inclusion criterion is intended to only capture patients with suspected CAD as confirmed by the currently accepted gold standard, coronary angiography.

- Referred patients must also have at least one prior abnormal test such as an abnormal exercise stress test, nuclear imaging or electrocardiogram PRIOR to coronary angiography referral.
- Patients must agree to provide their angiographic results as routinely captured on the participating hospitals Cardiac Catheterization Consult Forms.
- Patient must agree to have their interactions audio-recorded (only clinical histories).
- Patient must provide written informed consent.

4.2.3 Exclusion Criteria for Patients

- Patients referred for coronary angiography for reasons other than diagnosing coronary artery disease such as valvular disease, arrhythmia or pre-operation.
- Patients unable to communicate their own symptoms (i.e. severe dementia).

4.2.4. Inclusion/Exclusion Criteria for Physicians

- Physicians must agree to being audio-recorded strictly for the purposes of the study.
- Participating physicians must provide written informed consent.

4.3 Data collection

Patients will be approached in the pre-catheterization clinic/area of each hospital to participate in the study. Once a patient is consented into the study and has agreed to be audio-recorded, an audio-recorder will be included with the patient's chart. Brief instructions to operate the audio-recorded and a one-page form capturing demographic information, including if this is the patient's first coronary angiography, will be provided with the audio-recorder. There is no further information required directly from the patient for the remaining duration of this study. Patients will receive the standard of care.

4.4 Collection of Coronary Angiography Results

The referred patient will undergo their scheduled coronary angiography, following the standard of care. Angiographic outcomes on every patient will be extracted from the forms that each hospital uses at their institution as part of their standard/ routine care. Permission to use the information yielded from coronary angiography consult form will have been granted by the patient at the time of consent. The results of the patient's coronary angiogram will be extracted by patient unique number from electronic chart review according to each institutions IRB approved standard of practice/protocols for using electronic health records.

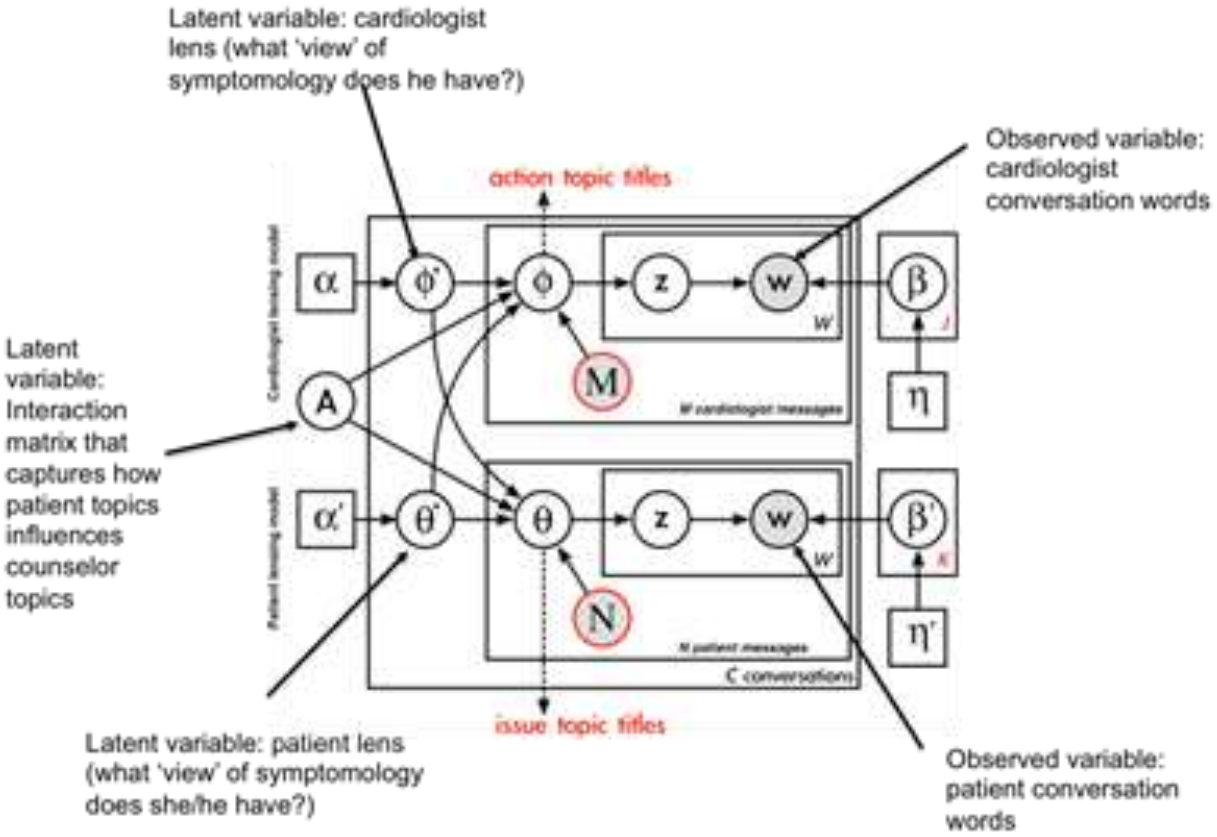
4.5 Discontinuation of Patients from the Study

All patients will be advised that their participation in the study is voluntary and they can withdraw from the study at any time, without having to provide a reason for doing so, or refuse to answer questions that make them feel uncomfortable. Patients who wish to withdraw from the study need not complete the recorded sessions.

5.0 Data Analysis

For this study we will treat the cardiologist-patient consultation as computational discourse formulation as the cardiologist and the patient converse about a shared set of topics. However, these topics will be viewed and generated through the unique perspective of two lenses; 1) from the cardiologist's perspective, who typically approach the conversation with a view of diagnosing, testing and treating the patient and 2) from the patient's perspective, who verbally express their symptoms with the hope of getting correctly diagnosed and treated. We will assess this discourse using a probabilistic generative topic model involving 'lensing' as we statistically extract the cardiologist and patient lenses from a corpus of real-world cardiologist-patient conversations. Furthermore, we will validate this conversation corpus against the ground truth or angiographic results of each patient, linking conversation, symptom expression and the diagnosis of coronary disease. We hypothesize that such a lensing analysis will **a)** statistically show a differential verbal expression of symptoms in both men and women for the same diagnosis of disease, and **b)** produce a three-stage hierarchical generative model of coronary disease, to symptomology, to the verbal expression of these symptoms, which can be used in reverse to predict the likelihood of coronary disease given a patients' verbal description of their symptoms.

The model is as follows:



6.0 Timeline

	May 2015	May-December 2015	September-October 2015	January-February 2016
Ethics Approval	x			
Patient recruitment & data collection *		x		
Interim analysis			x	
Statistical analysis				x
Report				x

*(depending on hospital volumes and recruitment success)

7.0 Ethical considerations

7.1 Informed Consent and Patient Information

All potential subjects eligible for the study will have the study described to them by a pre-catheterization clinic/area nurse/research assistant with sufficient information so that patients and physicians are able to make an informed decision about their participation in the study. Ample time for patients and physicians to decide will be provided, answering any questions they may have. The consent form with the protocol for review will be submitted to each participating hospital IRB committee by January 2015. The patient's most responsible physician will be notified that the patient has agreed to participate in our study.

7.2 Documentation

At the end of the study, the file matching the patient's name and ID number will be destroyed. The demographic data will be stored for ten years, as recommended by the research ethics committee, in a locked filing cabinet. All data sheets will be shredded to ensure confidentiality.

7.3 Confidentiality

Each participating patient will be given a numeric research ID number. This research ID number will be matched with the name of the patient, hospital unique number and zip/postal code so as to be able to link the patient with the angiographic results form. This information will be password protected and accessible by the principal investigators and research assistant. Demographic data will be stored in separate secure and locked filing cabinet. Data will be entered into an excel file by using ID numbers only (research ID number and hospital unique number). Only the investigators and research assistant will have access to the data.

8.0 Study Investigators

(1) Dr. Catherine Kreatsoulas,
Principal Investigator, Harvard T.H. Chan School of Public Health

(2) Karthik Dinakar,
Reid Hoffman Fellow & PhD Candidate, Co-investigator, MIT

(3) Dr. Deepak Bhatt,
Executive Director of Interventional Cardiovascular Programs, Professor of Medicine, Harvard University

(4) Dr. Shamir Mehta,
Director, Interventional Cardiology, Hamilton General Hospital, Professor of Medicine, McMaster University

(5) Dr. Christopher Buller,
Director, Interventional Cardiology and Catheterization Laboratory, St. Michael's Hospital, Professor of Medicine, University of Toronto

(6) Dr. Eric Horvitz,
Director, Microsoft Research

(7) Dr. Rosalind Picard,
Professor, MIT Media Lab

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