ASSOCIATION BETWEEN MYOCARDIAL ISCHEMIA, MICROVASCULAR FUNCTION AND PATIENT-REPORTED ANGINA

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MASTER OF SCIENCE

by
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ASSOCIATION BETWEEN MYOCARDIAL ISCHEMIA, MICROVASCULAR FUNCTION AND PATIENT-REPORTED ANGINA

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University of Missouri-Kansas City, 2018

ABSTRACT

Prior studies have not found an association between myocardial ischemia and measures of health status. Whether positron emission tomography (PET)-derived coronary flow reserve (CFR) would be better correlated with burden of angina is currently unknown. Understanding the relationship between myocardial ischemia, flow reserve and health status may illuminate how these variables can be used to inform post-test decisions.

Patients with known CAD referred for a clinically-indicated vasodilator PET myocardial perfusion imaging (MPI) between June 2009 and August 2013 who completed the Seattle Angina Questionnaire (SAQ) at the time of MPI and had available CFR data were identified. Angina frequency was determined using SAQ Angina Frequency scores according to previously published thresholds (none, monthly or weekly/daily; SAQ scores of 100, 61-99 and ≤ 60, respectively). The association between CFR and angina frequency was determined after adjusting for age, gender, and the presence of ischemia using ordinal logistic regression.

A total of 171 patients met inclusion criteria (mean age 66.3 ± 10.2 years; 61% men). Angina occurred on daily to weekly basis in 44 (25.7%) patients and monthly in 77 (45%) patients. Unadjusted mean CFR did not vary significantly across the spectrum of anginal burden (P=0.28). In the adjusted model, there was a significant interaction between ischemia and CFR (P value = 0.015), such that higher CFR was associated with lower angina

frequency only in patients with ischemia (OR per 1-unit increase in CFR 0.45 (95% CI [0.26-0.83], p=0.007), but not in those without ischemia (OR 1.10 (95% CI [0.63-2.00], p=0.85).

PET-derived CFR modulates the association between the presence of ischemia and the frequency of patient-reported angina, and complements ischemia in identifying patients with greater frequency of angina.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Medicine have examined a thesis titled “Association Between Myocardial Ischemia, Microvascular Function and Patient-Reported Angina” presented by Firas Al Badarin, candidate for the Master of Science degree, and certify that in their opinion it is worthy of acceptance.

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DEDICATION

This work is dedicated to my late dad, who never missed an opportunity during his life to instill in me the importance of perseverance and hard work as the means to achieve success and excellence. He also never failed to emphasize that there is no better pursuit than seeking knowledge and excellence in helping others. Dear dad, may your soul rest in peace.

CHAPTER 1

INTRODUCTION

Epidemiology of coronary artery disease

Despite major improvements in the identification and treatment of patients with coronary artery disease (CAD), heart disease continues to be the most common cause of death in the United States and other developed countries.[1,2] The death toll in the United States alone is greater than 366,000 lives per year, or more than 1000 deaths on average per day.[1] Additionally, caring for patients with CAD places enormous financial pressure on healthcare systems; estimated total CAD-related healthcare costs in the U.S. exceeded $200 billion in 2013, including expenses associated with testing, procedures, medications and loss of productivity in afflicted individuals.[1] Moreover, CAD has evolved into a global problem of epic proportions with substantial human and financial consequences worldwide,[1,3] with more than 110,00 million individuals worldwide estimated to have ischemic heart disease and almost 9 million attributable deaths around the world.[1] Despite being a global problem, prevalence of heart disease varies across the world, with significantly higher prevalence of ischemic heart disease in Russia and Eastern European countries (average 4000 cases/ 100,000 population); almost a 4-fold higher prevalence compared to Northern American countries (500-1000 cases/ 100,000 population), **Figure 1**.

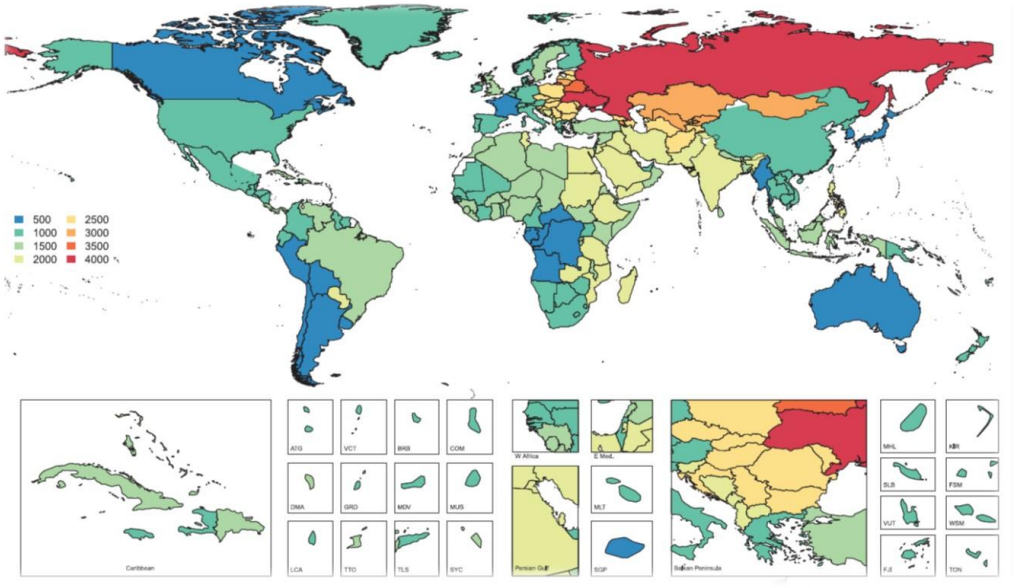


Figure 1: Global prevalence of coronary heart disease. The highest prevalence of ischemic heart disease worldwide is in Russia (4,000 cases per 100,000 on average), followed by countries in Northeast Asia and Eastern Europe (average 3,000 cases per 100,000). Corresponding prevalence in the U.S. is 1,000 cases per 100,000.

Atherosclerosis—development of cholesterol-laden plaque underneath the lining of coronary arteries, leading to pathological narrowing of coronary vessels—is the implicated process in the pathogenesis of CAD.[4] Symptomatic manifestations of CAD are variable, but angina pectoris remains one of the key CAD-related symptoms. Angina is typically described by patients as pressure, squeezing, vise-like or crushing sensation in the central chest, neck or shoulder areas. The term angina pectoris was first coined by William Heberden in 1772, who in his description mentioned "*But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it and the sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris*".[5] Angina is serious healthcare problem, affecting 3.4% of adults older than 20 years of age in the United States, with more than 560,000 new patients reporting angina every

year.[1] Moreover, angina is a major determinant of quality of life and a predictor of adverse cardiac events in patients with CAD.[6,7]

Myocardial ischemia, an imbalance between myocardial oxygen demand and supply is the mechanism implicated in the genesis of angina,[8] with ischemia leading to the perception of angina through stimulation of various chemical and mechano-receptors within the myocardium (**Figure 2**). Neuronal pathways involved in the perception of anginal pain are initiated via nerve fibers within the myocardium and those surrounding coronary blood vessels, that ultimately join the lower cervical and upper thoracic sympathetic ganglia.[9] At the cellular level, ischemia results in acidosis secondary to accumulation of lactic acid within the cell and in lower availability of ATP. This in turn leads to impaired function of the Na-K ATPase pump that maintains an electric gradient across the cell membrane, which then leads to abnormal handling of intracellular sodium and calcium. The release of adenosine is believed to be an important mediator of the initiation of neuronal impulses that ultimately lead to the perception of angina.[10]

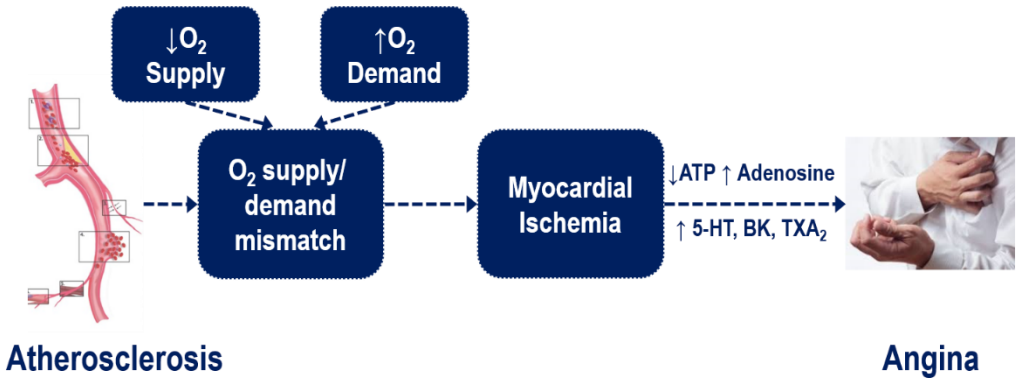


Figure 2: Mechanism of ischemia showing the link between atherosclerosis in epicardial coronary arteries and development of angina by patients (adapted from Frishman et al).[11]

The availability of innovative imaging technologies has provided reliable means for detecting the presence and magnitude of myocardial ischemia by capturing various manifestations of ischemia non-invasively.[12] The concept that ischemia-related derangements in cardiac physiology vary based on the duration and intensity of ischemic is referred to as the 'ischemic cascade'.[13] Development of regional myocardial perfusion abnormalities is an early event along this cascade, which could be captured with radionuclide scintigraphy, either using single photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging technologies. Perfusion imaging involves comparison of relative regional radiotracer uptake within the heart. Regional perfusion abnormalities under hyperemic conditions, typically seen as 'reversible perfusion defects' on a PET or SPECT myocardial perfusion study, are seen in myocardial territories subtended by epicardial coronary vessels that harbor significant, flow-limiting stenoses (**Figure 3**). In addition to detection of perfusion deficits, techniques such as PET also allow the detection of changes in left ventricular systolic function in response to increased myocardial blood flow and, as will be explained later, provides a reliable non-invasive assessment of coronary microvascular function.[14]

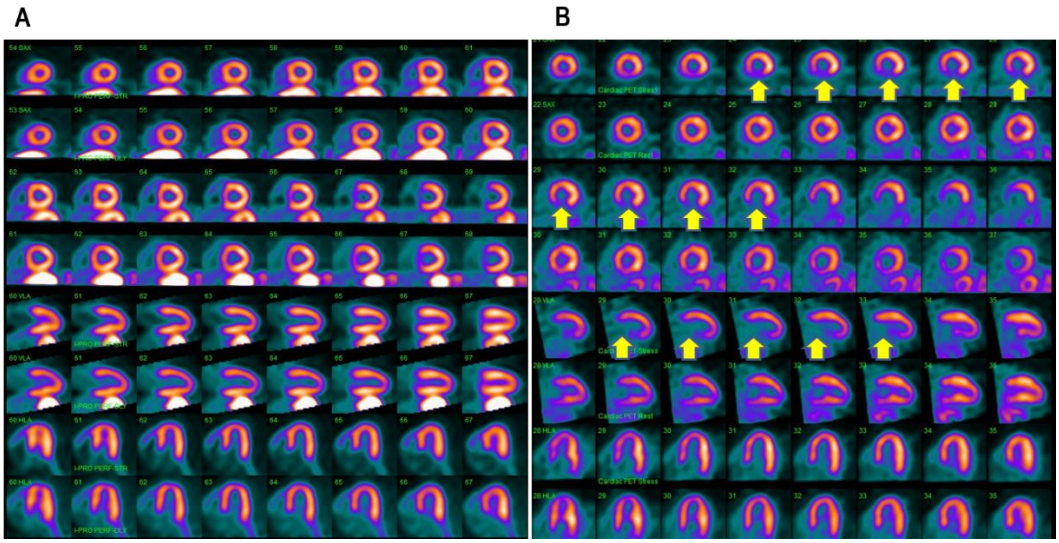


Figure 3: Representative examples of (A) normal PET myocardial perfusion study and (B) abnormal study showing a large area of ischemia (arrow heads) involving the inferior wall of the left ventricle.

Despite this biologically plausible link between myocardial ischemia and angina, prior studies have not documented an association between noninvasive measures of myocardial ischemia and the frequency of patient-reported anginal symptoms,[15-17] suggesting this relationship is probably more complex and likely modulated by other physiologic and psychosocial factors.

Structure and function of coronary microcirculation

More recently, the importance of the coronary microvasculature and its role in regulating myocardial blood flow has become more widely recognized.[18,19] It is currently largely believed that the coronary arterial system comprises 3 distinct components that each have a different function and is under control by different regulatory mechanisms (**Figure 4**).[20] The large epicardial vessels (>400 μm) serve the 'transport' function and offer minimal resistance to blood flow. Pre-arterioles (100-400 μm) and arterioles (40-100 μm), on the

other hand, are the 2 downstream components of the coronary circuit that are responsible for myocardial blood flow regulation, via changes in resistance to blood flow in response to humoral and metabolic signals in the local milieu. [19] These regulatory mechanism help ensure adequate myocardial blood flow under various conditions, thereby avoiding ischemia.

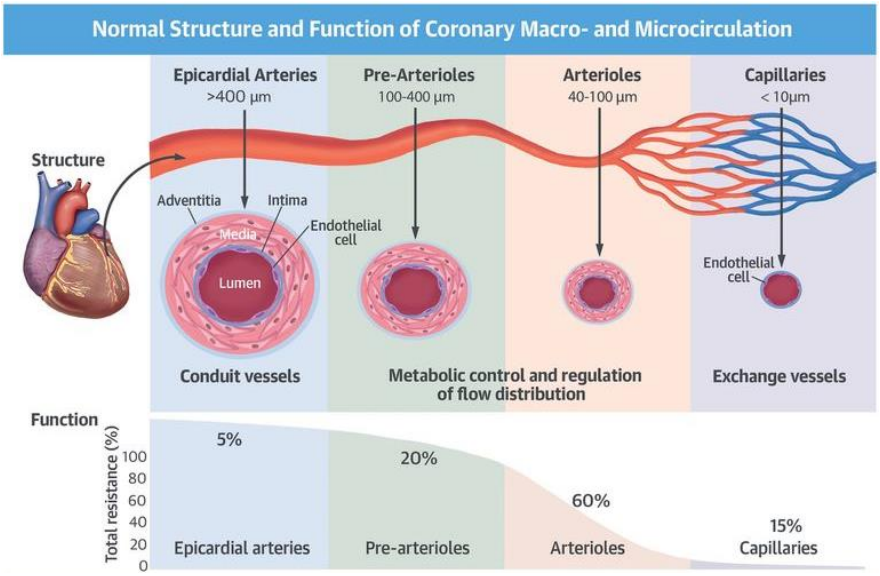


Figure 4: Schematic depiction of the coronary vascular system showing the various components and their respective functions and regulatory mechanisms (adapted from Taqueti et al).[19]

The contribution of coronary microvascular dysfunction to myocardial ischemia has been described in a variety of cardiovascular conditions, including those that involve obstructive epicardial coronary disease due to atherosclerosis as well as other conditions with various different mechanisms.[21] Therefore, coronary vasomotor function evaluation has become part of the diagnostic assessment of symptomatic patients with known or suspected CAD, using available invasive and non-invasive methods,[22] such as PET, cardiac magnetic resonance and transthoracic Doppler echocardiography.[23]

Role of cardiac PET in assessment of coronary microvasculature

Long considered a research tool, PET is now an imaging technology with versatile clinical applications across various disciplines in medicine, including cardiology, oncology and neurology.[24] As access to PET systems increases across practice settings, the use of this technology will continue to grow, primarily to offer non-invasive assessment of myocardial perfusion and function in patients with known or suspected CAD.[14] In addition to its diagnostic applications, PET myocardial perfusion imaging (MPI) can also provide prognostic information and helps stratify patients according to their risk of future adverse cardiovascular events.[25] Therefore, PET MPI is currently recommended in a wide array of clinical scenarios, particularly where high diagnostic accuracy and ability to predict future cardiovascular risk are highly desired, including patients with diabetes, women and those with suspected CAD involving the left main coronary artery.[26] Moreover, PET offers various advantages when compared to other modalities, such as SPECT, including superior diagnostic performance in detecting obstructive CAD, improved image quality and lower radiation exposure to patients.[27-30]

The ability to quantify absolute myocardial blood flow (MBF) is one of the most powerful applications of PET technology.[31] Assessing the functional integrity of the coronary microcirculation is currently the alternative to anatomic evaluation of coronary microvascular structures, since their size precludes *in vivo* imaging using traditional modalities. Coronary flow reserve (CFR) is a marker of coronary microvascular health and reflects the ability of the coronary circulation to augment blood flow in response to external stimuli.[32] Assessment of global myocardial blood flow at rest and under hyperemic conditions (following administration of vasodilators such as adenosine, regadenoson or dipyridamole) is currently

feasible in routine clinical practice.[33] CFR is then calculated as the ratio between absolute MBF at peak hyperemia and at rest. Such PET-derived flow measurements provide valuable information that improve the diagnostic and prognostic yields of MPI beyond routine assessment of relative perfusion patterns.[34-40] Moreover, CFR is associated with future cardiovascular events beyond hyperemic global MBF,[41] and therefore, has been a widely accepted surrogate of coronary microvascular status.

The 'missing' link between ischemia and angina

The occurrence of perfusion defects precedes the development of clinical symptoms, including angina along the ischemic cascade. Therefore, the lack of association between 'perfusion defects' and angina—a more downstream event—may at first be expected. However, a critical step in the development of ischemia, and subsequently angina, is impaired ability of the coronary microvasculature to dilate in response to increased myocardial oxygen demand, thereby leading to an imbalance between oxygen supply and demand. Consequently, it is conceivable that PET may be a better imaging technology to examine the relationship between ischemia and angina due to the unique opportunity to additionally evaluate coronary flow reserve and myocardial blood flow during stress non-invasively.

Whether PET-derived CFR is associated with the degree of patient-reported angina has not been previously established. Clarifying the interaction between CFR, the extent of myocardial ischemia and patients' symptoms will advance our knowledge about mechanistic pathways underlying angina development. Moreover, this can also illuminate how health status measures can be used to complement non-invasive markers of coronary physiology in

informing management decisions in patients with coronary disease. Accordingly, we sought to examine the association between coronary microvascular function, using PET-determined CFR, myocardial ischemia and patient-reported angina in a subset of symptomatic patients with known CAD.

CHAPTER 2

METHODS

Study participants and data source

This was a secondary analysis of data acquired in the context of a randomized clinical trial (NCT00976053). Briefly, patients with prior CAD who were referred for a clinically-indicated vasodilator PET MPI at the nuclear laboratory of Saint Luke's Mid America Heart Institute (Kansas City, MO) between June 2009 and August 2013 were eligible for enrollment if they met the study inclusion and exclusion criteria. All included subjects had prior history of CAD, defined as prior myocardial infarction or coronary revascularization >6 months prior to date of index test, and presented for evaluation of new symptoms suggestive of underlying ischemia, including chest pain or shortness of breath. Pregnant patients, those with BMI >38, left ventricular ejection fraction <40%, serum creatinine >2.5 mg/dL or severe valvular heart disease and those who received percutaneous coronary revascularization within 6 months of the index test were excluded. After screening, eligible patients provided informed consent and were enrolled in the study. The research study was reviewed and approved by the Saint-Luke's Institutional Review Board.

Health status assessment

All subjects completed an in-person assessment of the frequency of anginal symptoms and their impact on quality of life at the time of MPI performance using the Seattle Angina Questionnaire (SAQ).[42] The SAQ is a validated instrument for assessment of patient-reported symptoms that has been previously shown to be valid, reproducible and

sensitive to clinical changes.[43] SAQ comprises a total of 19 questions that quantify the impact of angina on patients' quality of life across 5 domains: Angina Frequency, Physical Limitation, Angina Stability, Treatment Satisfaction and Quality of Life. Each question is scored on an ordinal scale 1-6 for questions in the Angina Frequency, Physical Limitation, Angina Stability domains, and 1-5 for questions in the Quality of Life domain. The answers to each item are converted to scores ranging from 0-100, with lower scores indicating worse and higher scores indicating better health status.

SAQ scores from the Angina Frequency domain were used to group subjects as follows: daily (≤30); weekly (31-60); monthly (61-99) and no symptoms (100). Similar score ranges were used in prior studies by our group. Due to the low frequency of subjects with daily angina in this study, such subjects were combined with those in the weekly angina group.

Coronary flow reserve assessment

PET-derived measurements of absolute MBF (in ml/min/g) were made at rest and at peak stress using commercially available and previously validated software (Imagen Q, Kansas City, MO).[33,44] The software uses a net-retention model and has previously been validated against other software based on 1- and 2-tissue compartment models.[33,45,46] After obtaining rest and stress MBF measurements, CFR was calculated as the ratio of stress MBF to rest MBF for the entire left ventricle.[31] Only global CFR was included in this analysis since CFR has been shown to have an incremental prognostic value over hyperemic MBF.[41]

During the study period, PET-derived CFR measurements were inconsistently available as the technology and protocols were gradually incorporated into routine practice.

Therefore, some study participants did not have available flow data and were excluded. In addition, those with prior coronary artery bypass surgery (CABG) were excluded for the purpose of this analysis, since interpretation of CFR measurements in post-CABG patients is less reliable.[31]

PET myocardial perfusion imaging procedures

All included subjects completed PET MPI imaging in accordance with published guidelines.[47] Imaging was completed either using a dedicated cardiac PET scanner (Siemens, Munich, Germany) or hybrid PET/CT system (Siemens, Munich, Germany). Pharmacologic stress was completed per standard protocol,[48] using either dipyridamole or regadenoson. Rb-82 was injected for both rest and stress acquisitions at a dose of 20-60 mCi each. QPS software (CSMC, LA, CA) was used for analysis of perfusion images. Left ventricular volumetric and functional measurements were determined using QGS software (CSMC, LA, CA). PET MPI studies were interpreted by an experienced nuclear cardiologist who was blinded to the results of SAQ, and to CFR measurements.

The extent of ischemia was recorded using a semi-quantitative method, where each of the 17-myocardial segments was scored on a (0-4) scale by visual inspection, with lower scores indicating more severe reduction in tracer uptake. Segments were scored both with stress and at rest. Subsequently, summed rest, summed stress and summed difference scores (SDS) (stress minus rest) were calculated by combining segmental scores. Percentage of ischemic myocardium was calculated by dividing the SDS by 68 and multiplying by 100%. For the purpose of this analysis, an arbitrary threshold of 5% or greater was used to define the presence of ischemia. The rationale behind choosing this threshold is to identify a group

of subjects with unequivocally ischemic scintigraphic response, with an SDS cut-off of 3 or greater. This SDS threshold corresponds to an ischemic burden of 4.4% based on the formula mentioned earlier; the number was then rounded off to 5%.

Statistical analysis

Baseline demographics, clinical characteristics and imaging findings for patients across the spectrum of angina frequency were presented as means ± standard deviation for continuous variables, and as counts and percentages for categorical variables. Analysis of variance (ANOVA) was used for comparison of continuous variables and x^2 test for categorical variables. When assumptions for parametric tests were not fulfilled, we used a non-parametric alternative (Kruskal-Wallis test).

In order to better understand the association between angina and CFR, we constructed a proportional odds model predicting the next higher category of angina frequency, including covariates known to be associated with the outcome variable (angina), based on prior literature (age, gender and ischemia). Additionally, other covariates were included in the model if they were associated with the frequency of angina in the univariate analysis. Lastly, we included the interaction between ischemia and CFR in the model to examine the interaction between CFR and ischemic burden on angina frequency.

All analyses were performed using JMP 14 (SAS Institute Inc., Cary, NC, USA). Syntax delineating analyses performed is enclosed as Appendix **Table A-1**

CHAPTER 3

RESULTS

Study population

A total of 322 patients with symptomatic CAD who underwent PET MPI (June 2009-August 2013) also completed SAQ at the time of MPI. Of them, 130 (40.4%) did not have available or interpretable dynamic data to calculate CFR and were excluded. Additionally, 21 (6.5%) patients were excluded due to prior history of coronary artery bypass surgery. The remaining 171 patients were included in this analysis (**Figure 5**).

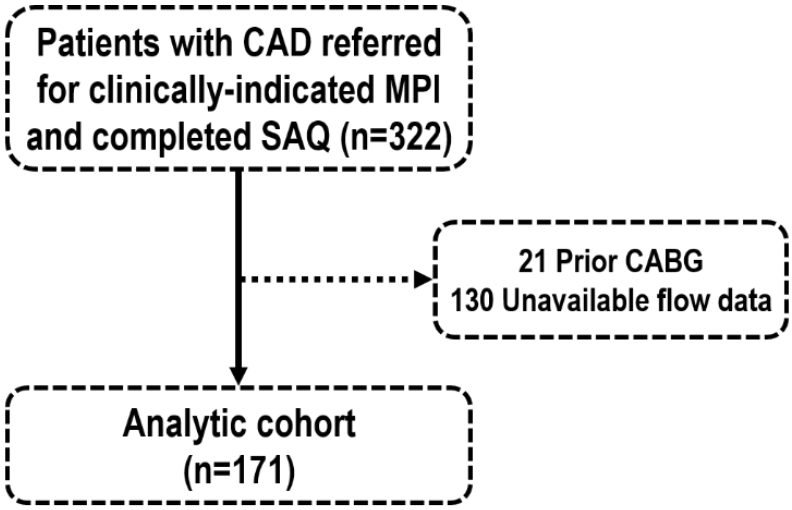


Figure 5: Flow diagram showing inclusion and exclusion criteria applied to define the study population.

The majority of subjects were men (61.4%), and the mean age was 66.3 ± 10.2 years. Most of the included subjects had hypertension (87.7%), and 1in 4 had diabetes. Chest pain was reported as a presenting symptom in 141 (82.4%) subjects, and dyspnea in 110 (64.3%) subjects. PET MPI revealed an ischemic burden >5% in 101 (59.1%) subjects and mean CFR in the overall cohort was 2.5 ± 0.7 (median 2.3; interquartile range 2-2.9).

According to SAQ Angina Frequency scores, 121 (70.8%) study participants reported some degree of angina, which was monthly in 77 (45.1%) and weekly or daily in the

remaining 44 (25.7%). Subjects with weekly or daily angina were younger compared to those with monthly or no angina (mean age 62.9 ± 9.7 vs. 65.7 ± 10.4 vs. 70.4 ± 9.2, respectively; P<0.001) and were more likely than those with no angina to be women (43% vs. 47% vs. 22%, respectively; P=0.02). Otherwise, baseline and clinical characteristics did not vary among patients across the angina frequency spectrum. **Table 1** summarizes baseline clinical and imaging characteristics and SAQ scores across the spectrum of angina frequency.

Table 1: Baseline clinical and imaging characteristics for study participants by frequency of angina

Variable	**None (n=50)**	**Monthly (n=77)**	**Weekly/ Daily (n=44)**	**P-value**
Age	70.4±9.2	65.7 ± 10.4	62.9 ± 9.7	0.001
Female (%)	11 (22%)	36 (47%)	19 (43%)	0.02
BMI	28.4±5.5	27.9 ± 4.2	28.3 ± 5	0.77
HTN (%)	45 (90)	64 (83)	41 (93)	0.27
DM (%)	8 (16)	18 (23)	16 (36)	0.07
Dyslipidemia (%)	50 (100)	77 (100)	44 (100)	1.00
Atrial fibrillation (%)	7 (16)	10 (13)	12 (24)	0.28
COPD (%)	6 (12)	11 (14)	10 (23)	0.34
Sleep apnea (%)	15 (30)	16 (21)	12 (27)	0.47
PVD (%)	16 (32)	18 (23)	15 (34)	0.37
Stroke (%)	27 (16)	13 (17)	6 (14)	0.89
CFR	2.6±0.8	2.4±0.7	2.4±0.8	0.28
SRS	2.7±4.1	2.5±3.6	2.5±5	0.93
SSS	8.4±6	7.9±6.2	5.8±5.4	0.07
SDS	5.9±4.2	5.6±4.2	3.5±2.8	0.005
% ischemia	8.7±6.2	8.2±6.1	5.1±4.1	0.005

Variable	None (n=50)	Monthly (n=77)	Weekly/ Daily (n=44)	P-value
LVEF stress (%)	55.2±12.3	57.8±12	56.1±10	0.43
LVEF rest (%)	50±11.8	52.1±12.4	50.3±10.2	0.56

BMI: body mass index; COPD: chronic obstructive pulmonary disease; CFR: coronary flow reserve; DM: diabetes mellitus; HTN: hypertension; PVD: peripheral vascular disease; SDS: summed difference score; SRS: summed rest score; SSS: summed stress score

Univariate association of ischemia and CFR with angina frequency

Mean CFR did not significantly vary by angina frequency in the unadjusted analysis: 2.4 ± 0.8 in patients with weekly/daily angina; 2.4 ± 0.7 in those with monthly angina and 2.6 ± 0.8 in those with no angina (P=0.28). Ischemic burden, on the other hand, was significantly lower in patients with weekly/daily angina compared with those who had monthly or no angina in the unadjusted analysis. Mean percent ischemic myocardium was 5.1 ± 4.1% in patients with most frequent angina, compared to 8.2 ± 6.1% and 8.7 ± 6.2% in those with monthly and no angina, respectively (P=0.005). When CFR was compared across the spectrum of angina frequency, there was a trend towards lower CFR in patients with weekly/daily angina compared to those with monthly or no angina (2.1 ± 0.5 vs. 2.4 ± 0.7 vs. 2.6 ± 0.8; P=0.08 for between-group difference) in patients with ≥5% ischemia, but not in those with <5% ischemic myocardium (2.7 ± 0.8 vs. 2.4 ± 0.78 vs. 2.8 ± 0.8; P=0.18 for between-group difference), **Figure 6**.

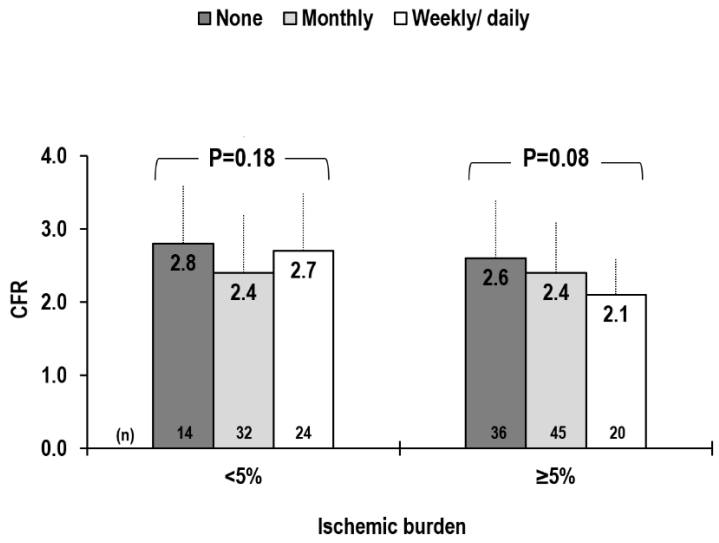
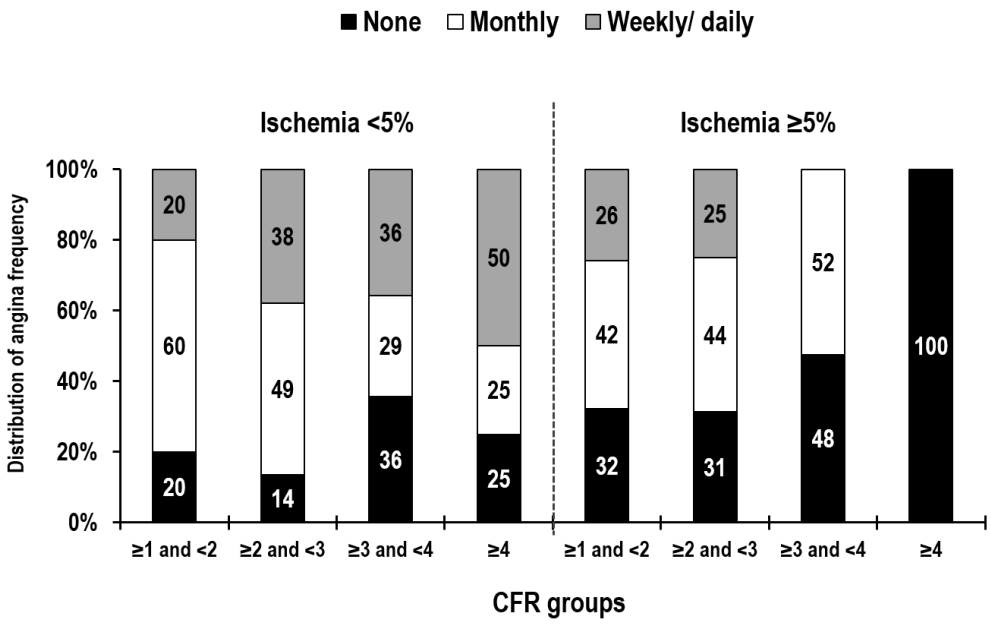


Figure 6: Mean coronary flow reserve by angina frequency in patients by extent of ischemic myocardium

We then examined the distribution of angina frequency across the CFR spectrum (expressed as 1-unit increments) in subjects with and without ischemia (**Figure 7**). In the presence of ischemia (≥5% ischemic burden), more patients had no or monthly angina as CFR increased, while more patients had weekly/ daily angina as CFR deceased (P=0.04). On the other hand, the distribution of angina frequency was not significantly different across the CFR spectrum when the ischemic burden was <5% (p=0.43).



N=	15	37	14	4	31	48	21	1
Median CFR	1.85	2.3	3.24	4.63	1.71	2.42	3.29	4.44

Figure 7: distribution of angina frequency across the CFR spectrum (displayed in 1-unit increments) in patients with and without ischemia

Adjusted association between CFR and ischemia with SAQ

In a proportional odds model adjusted for age, gender, ischemic burden, CFR and ischemic*CFR interaction constructed to understand the influence of both ischemia and CFR on angina, age and gender were independent predictors of angina frequency, such that older patients were significantly less likely to have more frequent angina (OR for 10-year increment in age is 0.52, 95% CI [0.40-0.71], P<0.001), whereas female patients were more likely to have more frequent angina (OR 1.44, 95% CI [1.07-1.96], P<0.001), **Table 2**.

Table 2: Independent predictors of angina frequency

Variable	OR (95% CI)	P-value
Age (+10)	0.52 (0.40-0.71)	<0.001
Female	1.44 (1.07-1.96)	0.02
Ischemia (+5%)	0.70 (0.52-0.88)	0.004
CFR	0.64 (0.42-0.98)	0.04
Ischemia*CFR	0.91 (0.85-0.98)	0.015

Model included age, gender, ischemia, CFR and interaction term ischemia*CFR
CFR: coronary flow reserve; OR: odds ratio

In addition, there was a significant interaction between ischemic burden and CFR on angina frequency (P value for the interaction= 0.015), such that higher CFR was associated with lower frequency of angina only in patients with ≥5% ischemic burden (OR for 1 unit increase in CFR is 0.45; 95%CI [0.26-0.83], P=0.007), but not in those with <5% ischemia (OR 1.1; 95%CI [0.63-2], P=0.85), **Figure 8**.

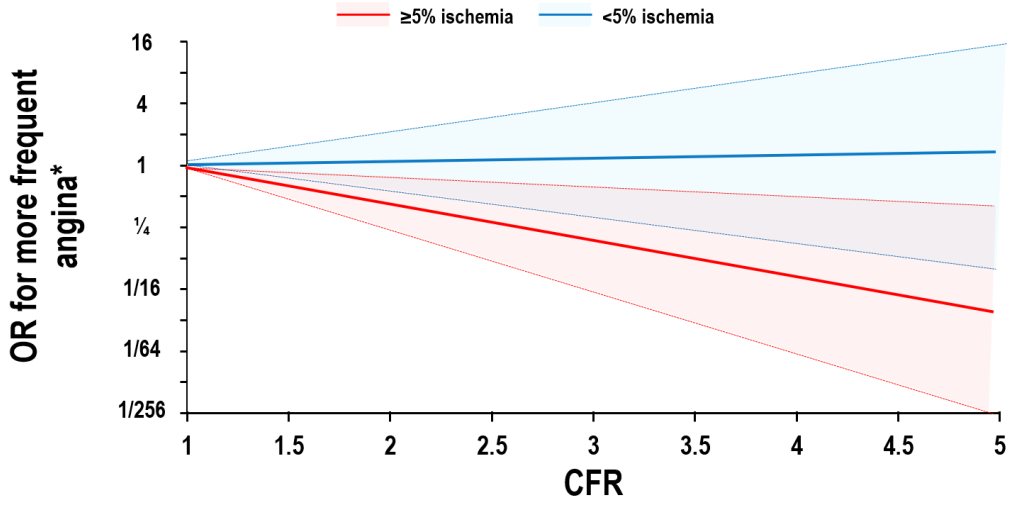


Figure 8: Interaction between coronary flow reserve and ischemic burden on likelihood of angina

CHAPTER 4

DISCUSSION

Untangling the complex interaction between myocardial ischemia and the degree of patient-reported symptoms remains an area of unmet need. The current data offer additional insight into this relationship by suggesting that CFR is associated with the frequency of reported angina in an ischemia-dependent fashion. When ischemic burden was absent or low, there was no association between the status of coronary circulation and patient-reported symptoms. Conversely, in the presence of myocardial ischemia, lower CFR—indicative of impaired ability to augment coronary flow in response to external stress—was associated with more angina. This suggests that the status of coronary vasomotor function might provide additional insight into understanding the impact of myocardial ischemia on health status in patients with CAD which will potentially advance our knowledge about a potential 'missing link' between ischemia and angina.

The following explanation can be posited for the current hypothesis-generating findings. When ischemia is present, the reduction in myocardial perfusion will cause a degree of angina that is also related to the coronary vasodilatory capacity. A patient with markedly impaired vasodilatory capacity—and hence lower CFR—will be less likely to augment their myocardial blood flow to meet the increasing demands for oxygen and will, therefore, have more profound angina, compared to another patient with a higher CFR, who would likely report less angina for the same magnitude of ischemia. On the other hand, lack of myocardial ischemia indicates the absence of myocardial oxygen supply-demand mismatch, thereby eliminating an early step in the cascade of angina perception. Under these circumstances, a change in CFR will not be associated with variation in angina frequency.

Growing evidence suggests that coronary microvasculature plays a pivotal role in regulating myocardial blood flow and in contributing to the development of ischemia.[21] In addition to patients with obstructive epicardial coronary disease, reduced coronary vasodilatory capacity is implicated in the pathogenesis of symptoms in a myriad of other cardiovascular conditions, including cardiomyopathies, amyloidosis and left ventricular hypertrophy.[22] Therefore, there has been growing interest in assessing coronary vasomotor function reliably using invasive and non-invasive techniques.[23] Non-invasive CFR measurement using cardiac PET perfusion analysis has made the detection of microvascular dysfunction and monitoring response to interventions feasible in the realm of routine clinical practices.[32] Moreover, flow quantification is currently recommended in a wide array of clinical indications,[31] with extensive applications particularly in ischemic heart disease patients.[34] As such, CFR has the potential to play important complementary role to other physiologic markers of ischemia in informing management decisions in patients with CAD.

Several prior investigations have examined the association between ischemia and burden of angina. Arnold et al showed no difference in the extent of perfusion abnormality across a range of SAQ scores in 191 patients with demonstrable ischemia on non-attenuation corrected SPECT MPI.[15] Similarly, the size of perfusion defect/ ischemia was not a predictor of health status measured using a generic health status instrument, the SF-36 Survey, in a cohort of 195 symptomatic patients referred for exercise SPECT MPI.[16] There are several potential explanations for this lack of association between the extent of perfusion abnormalities and health status in earlier studies. First, since the occurrence of perfusion abnormalities is an early event in the ischemic cascade that precedes clinical symptoms, it plausible that not all perfusion abnormalities will be accompanied with anginal symptoms.

Second, prior studies have included patients who were tested with non-attenuation corrected SPECT MPI, which is known to have modest diagnostic accuracy. Therefore, the apparent perfusion abnormalities may represent soft attenuation, rather than true abnormalities with myocardial perfusion.

Unlike prior studies, we were able to expand analyses to include coronary microcirculatory status and were able to show that the effect of ischemia on quality of life is modulated by CFR. For 2 patients with a similar ischemic burden, the impact of myocardial ischemia on quality of life is expected to be more magnified in the patient with worse coronary vasomotor function, manifesting as lower CFR.

Clinical Implications and Future Directions

There are several potential clinical implications for the current findings after prospective validation in larger and more generalizable samples. First, knowledge of the coronary microcirculation status will complement knowledge about the presence and extent of ischemia in better describing the true impact of CAD on patients' symptomatic status; for the same degree of ischemia, a patient with a higher CFR will likely have less angina compared to someone with lower CFR. Second, understanding how the addition of coronary vasomotor function to the burden of ischemia helps identify patients who are likely to benefit from coronary revascularization is another intriguing concept that was evaluated recently, while the ischemia-directed approach to revascularization is being tested in large randomize clinical trials (NCT01471522).[49]

Study limitations

Our findings need to be interpreted in the context of the following limitations. First, small sample size may affect confidence limits around the point estimates in our results and, therefore, these findings should be considered hypothesis-generating. Nevertheless, this is the first demonstration, to our knowledge, of an interaction between ischemia, CFR and patient-reported angina. Second, patients included in this analysis were highly selected patients, predominantly comprising stable patients in the outpatient setting. Such patients may be of relatively lower risk compared to other patient populations with prior CAD. Whether those findings can be extrapolated to other populations is uncertain.

CHAPTER 5

CONCLUSION

The relation between ischemia and health status is complex and involves an interaction with coronary microvascular function. In the presence of myocardial ischemia, worse coronary flow reserve is associated with more frequent angina. Conversely, when myocardial ischemia was absent there was not an association between coronary flow reserve and angina symptoms, suggesting that both myocardial ischemia and coronary vasomotor function are intricately related in modulating the impact of CAD on health status.

APPENDIX

A.1 JMP Program Syntax Delineating Codes for This Papers Analyses

Comparison of baseline characteristics:

```
Fit Group(
	Oneway(
		Y( :Age ),
		X( :Angina freq ),
		Means( 1 ),
		Means and Std Dev( 1 ),
		Mean Diamonds( 1 ),
		Mean Error Bars( 1 ),
		Std Dev Lines( 1 )
	),
	Oneway( Y( :BMI ), X( :Angina freq ) ),
	Contingency( Y( :Gender ), X( :Angina freq ), Contingency Table ),
	Contingency( Y( :CP ), X( :Angina freq ), Contingency Table ),
	Contingency( Y( :SOB ), X( :Angina freq ), Contingency Table ),
	Contingency( Y( :dyspnea ), X( :Angina freq ), Contingency Table ),
	Contingency( Y( :Lipids ), X( :Angina freq ), Contingency Table ),
	Contingency( Y( :HTN ), X( :Angina freq ), Contingency Table ),
	Contingency( Y( :DM 2 ), X( :Angina freq ), Contingency Table ),
	Contingency( Y( :Name( "PSVT/SFib" ) ), X( :Angina freq ), Contingency Table ),
	Contingency( Y( :COPD ), X( :Angina freq ), Contingency Table ),
	Contingency( Y( :Sleep Apnea ), X( :Angina freq ), Contingency Table ),
	Contingency( Y( :CVD ), X( :Angina freq ), Contingency Table ),
	Contingency( Y( :PVD ), X( :Angina freq ), Contingency Table ),
	Oneway( Y( :CFR ), X( :Angina freq ) ),
	Oneway( Y( :PET_% ischemia_Quan ), X( :Angina freq ) ),
	Oneway( Y( :PET_SSS_Quan ), X( :Angina freq ) ),
	Oneway( Y( :PET_SRS_Quan ), X( :Angina freq ) ),
	Oneway( Y( :PET_SDS_Quan ), X( :Angina freq ) ),
	<<{Arrange in Rows( 1 )}
);

Oneway(
	Y( :CFR ),
	X( :Angina freq ),
	Means( 1 ),
	Means and Std Dev( 1 ),
	Mean Diamonds( 1 ),
	Mean Error Bars( 1 ),
	Std Dev Lines( 1 ),
	Where( :ischemia GTE 5% == 0 )
);
```

Proportional odds model for independent predictors of angina frequency:

```
Fit Model(
	Y( :Angina freq ),
	Effects(
		:CFR,
		:PET_% ischemia_Quan,
		:Age,
		:Gender,
		:CFR * :PET_% ischemia_Quan
```

```
),
Personality( "Ordinal Logistic" ),
Run(
	Confidence Intervals( 1 ),
	Likelihood Ratio Tests( 1 ),
	Profiler(
		1,
		Interaction Profiler( 1 ),
		Term Value(
			CFR(
				2.4795,
				Min( 0.570823529411765 ),
				Max( 5.17882352941177 ),
				Lock( 0 ),
				Show( 1 )
			),
			PET_% ischemia_Quan( 7.551, Lock( 0 ), Show( 1 ) ),
			Age( 66.281, Lock( 0 ), Show( 1 ) ),
			Gender( 2, Lock( 0 ), Show( 1 ) )
```

REFERENCE LIST

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association. *Circulation.* 2018; 137:e67-e492..

2. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med.* 2007;356(23):2388-2398.

3. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. *Ann Transl Med.* 2016;4(13):256.

4. Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. *Nat Med.* 2011;17(11):1410-1422.

5. W H. Some account of a disorder of the breast. *Medical Transactions The Royal College of Physicians of London.* 1772(2):59-67.

6. Steg PG, Greenlaw N, Tendera M, et al. Prevalence of anginal symptoms and myocardial ischemia and their effect on clinical outcomes in outpatients with stable coronary artery disease: data from the International Observational CLARIFY Registry. *JAMA Intern Med.* 2014;174(10):1651-1659.

7. Kones R, Rumana U. Angina may trump ischaemia in predicting stable coronary artery disease outcomes, but most cardiovascular events occur in patients without angina or asymptomatic ischaemia. *Evidence-based medicine.* 2015;20(3):111.

8. Conti CR. Re-thinking angina. *Clin Cardio.l* 2007;30(2 Suppl 1):I1-3.

9. Foreman RD. Mechanisms of cardiac pain. *Annu Rev Physiol.* 1999;61:143-167.

10. Lagerqvist B, Sylven C, Beermann B, Helmius G, Waldenstrom A. Intracoronary adenosine causes angina pectoris like pain--an inquiry into the nature of visceral pain. *Cardiovasc Res.* 1990;24(8):609-613.

11. Frishman WH. Pharmacology of the nitrates in angina pectoris. *Am J Cardiol.* 1985;56(17):8I-13I.

12. Pontone G, Guaricci AI, Neglia D, Andreini D. State of the art: non-invasive imaging in ischaemic heart disease. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology.* 2017;13(6):654-665.

13. Schuijf JD, Shaw LJ, Wijns W, et al. Cardiac imaging in coronary artery disease: differing modalities. *Heart (British Cardiac Society).* 2005;91(8):1110-1117.

14. Al-Mallah MH, Sitek A, Moore SC, Di Carli M, Dorbala S. Assessment of myocardial perfusion and function with PET and PET/CT. *J Nucl Cardiol.* 2010;17(3):498-513.

15. Arnold SV, Spertus JA, Ciechanowski PS, et al. Psychosocial modulators of angina response to myocardial ischemia. *Circulation.* 2009;120(2):126-133.

16. Mattera JA, De Leon CM, Wackers FJ, Williams CS, Wang Y, Krumholz HM. Association of patients' perception of health status and exercise electrocardiogram, myocardial perfusion imaging, and ventricular function measures. *Am Heart J.* 2000;140(3):409-418.

17. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. *JAMA.* 2003;290(2):215-221.

18. Pries AR, Badimon L, Bugiardini R, et al. Coronary vascular regulation, remodelling, and collateralization: mechanisms and clinical implications on behalf of the working group on coronary pathophysiology and microcirculation. *Eur Heart J.* 2015;36(45):3134-3146.

19. Taqueti VR, Di Carli MF. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2018;72(21):2625-2641.

20. De Bruyne B, Oldroyd KG, Pijls NHJ. Microvascular (Dys)Function and Clinical Outcome in Stable Coronary Disease. *J Am Coll Cardiol.* 2016;67(10):1170-1172.

21. Kaski JC, Crea F, Gersh BJ, Camici PG. Reappraisal of Ischemic Heart Disease. *Circulation.* 2018;138(14):1463-1480.

22. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med.* 2007;356(8):830-840.

23. Camici PG, d'Amati G, Rimoldi O. Coronary microvascular dysfunction: mechanisms and functional assessment. *Nat Rev Cardiol.* 2015;12(1):48-62.

24. Beadsmoore C, Newman D, MacIver D, Pawaroo D. Positron Emission Tomography Computed Tomography: A Guide for the General Radiologist. *Canadian Association of RadiologistsJournal = Journal l'Association canadienne des radiologistes.* 2015;66(4):332-347.

25. Dorbala S, Di Carli MF. Cardiac PET perfusion: prognosis, risk stratification, and clinical management. *Semin Nucl Med.* 2014;44(5):344-357.

26. Bateman TM, Dilsizian V, Beanlands RS, DePuey EG, Heller GV, Wolinsky DA. American Society of Nuclear Cardiology and Society of Nuclear Medicine and

Molecular Imaging Joint Position Statement on the Clinical Indications for Myocardial Perfusion PET. *J Nucl Med.* 2016;57(10):1654-1656.

27. Danad I, Raijmakers PG, Driessen RS, et al. Comparison of Coronary CT Angiography, SPECT, PET, and Hybrid Imaging for Diagnosis of Ischemic Heart Disease Determined by Fractional Flow Reserve. *JAMA Cardiol.* 2017;2(10):1100-1107.

28. Mc Ardle BA, Dowsley TF, deKemp RA, Wells GA, Beanlands RS. Does rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease?: A systematic review and meta-analysis. *J Am Coll Cardiol.* 2012;60(18):1828-1837.

29. Cerqueira MD, Allman KC, Ficaro EP, et al. Recommendations for reducing radiation exposure in myocardial perfusion imaging. *J Nucl Cardiol.* 2010;17(4):709-718.

30. Bateman TM, Heller GV, McGhie AI, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. *J Nucl Cardiol.* 2006;13(1):24-33.

31. Murthy VL, Bateman TM, Beanlands RS, et al. Clinical Quantification of Myocardial Blood Flow Using PET: Joint Position Paper of the SNMMI Cardiovascular Council and the ASNC. *J Nucl Med.* 2018;59(2):273-293.

32. Schindler TH, Schelbert HR, Quercioli A, Dilsizian V. Cardiac PET imaging for the detection and monitoring of coronary artery disease and microvascular health. *JACC Cardiovasc Imaging.* 2010;3(6):623-640.

33. Nesterov SV, Deshayes E, Sciagra R, et al. Quantification of myocardial blood flow in absolute terms using (82)Rb PET imaging: the RUBY-10 Study. *JACC Cardiovasc Imaging.* 2014;7(11):1119-1127.

34. Al Badarin F, Aljizeeri A, Almasoudi F, Al-Mallah MH. Assessment of myocardial blood flow and coronary flow reserve with positron emission tomography in ischemic heart disease: current state and future directions. *Heart Fail Rev.* 2017;22(4):441-453.

35. Naya M, Murthy VL, Taqueti VR, et al. Preserved coronary flow reserve effectively excludes high-risk coronary artery disease on angiography. *J Nucl Med.* 2014;55(2):248-255.

36. Ziadi MC, Dekemp RA, Williams K, et al. Does quantification of myocardial flow reserve using rubidium-82 positron emission tomography facilitate detection of multivessel coronary artery disease? *J Nucl Cardiol.* 2012;19(4):670-680.

37. Ziadi MC, Dekemp RA, Williams KA, et al. Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia. *J Am Coll Cardiol.* 2011;58(7):740-748.

38. Fukushima K, Javadi MS, Higuchi T, et al. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical 82Rb PET perfusion imaging. *J Nucl Med.* 2011;52(5):726-732.

39. Herzog BA, Husmann L, Valenta I, et al. Long-term prognostic value of 13N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. *J Am Coll Cardiol.* 2009;54(2):150-156.

40. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation.* 2011;124(20):2215-2224.

41. Gupta A, Taqueti VR, van de Hoef TP, et al. Integrated Noninvasive Physiological Assessment of Coronary Circulatory Function and Impact on Cardiovascular Mortality in Patients With Stable Coronary Artery Disease. *Circulation.* 2017;136(24):2325-2336.

42. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol.* 1995;25(2):333-341.

43. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Fihn SD. Monitoring the quality of life in patients with coronary artery disease. *Am J Cardiol.* 1994;74(12):1240-1244.

44. Yoshida K, Mullani N, Gould KL. Coronary flow and flow reserve by PET simplified for clinical applications using rubidium-82 or nitrogen-13-ammonia. *J Nucl Med.* 1996;37(10):1701-1712.

45. Lortie M, Beanlands RS, Yoshinaga K, Klein R, Dasilva JN, DeKemp RA. Quantification of myocardial blood flow with 82Rb dynamic PET imaging. *Eur J Nucl Med Mol Imaging.* 2007;34(11):1765-1774.

46. Herrero P, Markham J, Shelton ME, Bergmann SR. Implementation and evaluation of a two-compartment model for quantification of myocardial perfusion with rubidium-82 and positron emission tomography. *Circ Res.* 1992;70(3):496-507.

47. Dilsizian V, Bacharach SL, Beanlands RS, et al. ASNC imaging guidelines/SNMMI procedure standard for positron emission tomography (PET) nuclear cardiology procedures. *J Nucl Cardiol.* 2016;23(5):1187-1226.

48. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. *J Nucl Cardiol.* 2016;23(3):606-639.

49. Maron DJ, Hochman JS, O'Brien SM, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: Rationale and design. *Am Heart J.* 2018;201:124-135.

VITA

Firas Al Badarin was born in Hebron/ West Bank on July 15th, 1978, to a general practitioner and a school teacher. Shortly after his birth, Firas moved with his family to the United Arab Emirates where his father practiced medicine and his mom taught English language for middle school for 14 years, before returning to Jordan where he completed high school and entered medical school at the University of Jordan in Amman, Jordan in 1996.

After graduation from medical school in 2002, Firas decided to pursue training in internal medicine and then in cardiology. Knowing that his best training options would be in United States, he took Medical License Examinations and joined the Internal Medicine program at Henry Ford Hospital in Detroit, MI in 2004, where he spent 4 years after acting as a chief medical resident. Afterwards, he completed a subspecialty training in preventive cardiology at the Mayo Clinic in Rochester, MN, followed by general cardiology training at Saint Luke's Mid America Heart Institute, University of Missouri- Kansas City.

Despite his strong desires to pursue further training in advanced cardiac imaging, he had to fulfill his Visa employment obligations and served in Carbondale, IL as a general cardiologist with the Prairie Cardiovascular Consultants Group. During practice, Firas has proven himself as a competent clinician, effective communicator and strong advocate for his beloved field of practice. However, he could not resist the urge to pursue his dream of becoming an academic cardiologist/ cardiac imager. That was when joined a T32 fellowship program in outcomes research and imaging at Saint Luke's Mid America Heart Institute and enrolled in the Master Program in Clinical Bioinformatics/ clinical research emphasis.