SATURATION

(SoutheAsT eUrope microciRculATION) registry

Study protocol version 1.3

Date 03/21/2024

Introduction

Ischemic heart disease is a leading cause of morbidity and mortality. While cardiologists are focused on discrete, visible stenoses of coronary arteries there is increasing awareness of the importance of microcirculation in causing angina. Microvascular bed is comprised of vessels smaller than 500 microns in diameter. Their network is much greater than the network of epicardial vessels and serves important functions such as regulation of myocardial blood flow and cellular metabolism.

Myocardial ischemia is usually caused by significant stenosis of the epicardial coronary artery. However, a study that included over 400000 coronary angiograms found that in over 50% of cases there was no obstructive coronary artery disease (CAD) or stenoses were less than 50%[1]. It was not until recently that the importance of coronary microcirculation in causing symptoms and signs of ischemia has been appreciated. Coronary microvascular dysfunction (CMD) has an important effect in determining patient outcomes in a number of clinical settings.

Invasive pressure measurements with coronary wire for measurement of pressure and temperature is a well-established technique in evaluating coronary artery stenoses. Using the same pressure wire, technological advances have allowed estimation of coronary artery flow using principles of thermodilution. This method has been validated in an experimental model, and also in humans, providing an excellent invasive tool in assessing coronary flow reserve (CFR). To assess microcirculation independently, index of microcirculatory resistance (IMR) has been developed. Assuming negligible coronary venous pressure, the resistance of coronary circulation can be calculated as distal coronary pressure (Pd) divided by absolute coronary flow, the latter being proportional to the inverse of mean hyperaemic transit time and thus allowing for calculation of IMR. IMR has been shown to be independent of epicardial coronary artery stenosis. It has been demonstrated that IMR can have predictive value in patients with ST elevation myocardial infarction. A distinct clinical entity known as ischemia with no obstructive coronary arteries (INOCA) has been developed to encompass the patients with clear angina symptoms, but without visible epicardial coronary artery stenoses.

The region of Southeast Europe has its specificities regarding morbidity and mortality from cardiovascular diseases. It includes transitional countries as well as Mediterranean countries where CV diseases are one of the major causes of morbidity. In this registry we wanted to evaluate the practice of patient selection for evaluation of microcirculatory bed, including indications, ischemia tests done, medications prescribed, procedural aspects of microcirculation

evaluation and treatment changes after testing. Also, we want to have an insight regarding adverse cardiovascular events in these patients after invasive coronary physiology.

Aims

Aim 1: To assess the regional practice of patient selection for assessment of invasive coronary physiology including vasospasm testing and estimation of microcirculation by measuring CFR and IMR.

Aim 2: To assess regional procedural aspects of invasive coronary physiology – how aforementioned parameters are measured in the catheterization laboratory

Aim 3: To assess patients' treatment and treatment changes after invasive coronary physiology measurements at each follow up visit.

Aim 4: To compare the cardiovascular outcomes and additional procedures (stress testing, angiography, etc.) done after comprehensive invasive coronary physiology evaluation.

Research design and methods

The study would be prospective, observational and will include patients that underwent invasive coronary physiology with Coroflow Coroventis Cardiovascular System software using Pressure Wire X (Abbott, Abbott Park, IL, US). Participants will undergo routine coronary angiography as well as comprehensive physiologic assessment coronary thermodilution to evaluate for coronary microvascular dysfunction (CMD) and possibly with provocative testing for diagnosis of vasospastic angina (VSA). The study will include centres in Southeast Europe that have obtained Coroventis Coroflow Cardiovascular system and have performed invasive coronary physiology procedures.

Inclusion Criteria

- Adults of both sexes older than 18 years
- Angina symptoms or angina equivalent
- Referred to Cath lab for evaluation of CAD
- Invasive physiology testing performed (microcirculation testing +/- vasospasm testing) using Coroflow Coroventis Cardiovascular system (Abbott, Abbott Park, IL, US)

Exclusion Criteria

- persons under the age of 18
- pregnant of nursing
- no coronary physiology measurements performed

Outcomes

Outcomes will be evaluated every 6 months for 2 years via direct patient contact by research staff or at follow up visits.

- Primary outcomes:
    - all-cause death and non-fatal MI
    - composite MACE: all-cause death, non-fatal MI, coronary revascularization, hospitalization for cardiovascular causes (acute coronary syndrome, heart failure, angina, repeated coronary angiography)
- Secondary outcomes: all-cause death, cardiovascular death, MI, coronary revascularization, stroke, hospitalization for heart failure, hospitalization for acute coronary syndrome, repeated coronary angiography
- Patient-centred outcomes
    - Freedom from angina (SAQ questionnaire)
    - Quality of life using EQ-5D-5L questionnaire
    - Follow up non-invasive ischemia testing (if performed)

Study protocol must be approved by the institutional Ethics committee prior to enrolling patients in the study. Patients will be enrolled in the study by the investigators familiar with the study protocol. Patients will be enrolled after invasive coronary physiology procedure. Patients will sign informed consent (IC) form provided and explained by the study team member. After signing IC form patients will be eligible for entering the study. Patients' treatment is responsibility of the treating physician and the participation in the study will not alter patients' treatment.

After enrolling the patients in the study, they will be treated according to local protocols and current recommendations for INOCA.

The patients' data will be stored in an online database managed by Castor EDC organization. Every centre will have the opportunity to access the database and enter patients' data into it. The data collected for a patient in the study will be the following:

Enrollment

1. **Demographics**

Date of birth

Date of invasive physiology assessment

Sex

Race

Height

Weight

BMI

Site of enrollment

2. **Risk factors**

Comorbidities

Recent lab studies

Smoking status

Family history of premature coronary disease

3. **Previous cardiovascular events**

Myocardial infarction (ever and in the past 30 days)

TIA/stroke

Other cardiovascular diseases

Prior angiographies

Prior PCIs

NYHA class

CCS class

4. **Medications**
5. **Baseline echocardiography**
6. **Non-invasive ischemia testing**
7. **Seattle Angina Questionnaire**
8. **EQ-5D-5L**

9. **Coronary angiography findings**

Presence of obstructive coronary artery disease (CAD)

Coronary vessel(s) with obstructive CAD

Previous PCI procedure in coronary vessel(s)

10. **Invasive physiology procedure**

Primary indication

Access site

Radial sheath medications

Withholding the calcium channel blocker, beta blocker, nitrate

Vasospastic angina testing (which artery, what test, result)

Microvascular angina testing (which artery, CFR, IMR, RRR, FFR, Pd, Pa and all transit times)

Complications

Follow up visit

1. **Demographics**
2. **Events (MACE)**
3. **Medications**
4. **SAQ**
5. **EQ-5D-5L**
6. **New non-invasive ischemia testing**

Author correspondence

Dr Ivan Ilic

Department of interventional cardiology

Cardiology clinic, Institute for cardiovascular diseases Dedinje,

Heroja Milana Tepica 1, 11040 Belgrade, Serbia

Email: Ivan1ilic@yahoo.com, phone +381(11) 3601-700; cell +381(64) 137-4455