Index of microcirculatory resistance evaluation in patients with Coronary Sinus Reducer Implantation for the treatment of chronic refractory Angina pectoris, the INROAD study

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Brief title:

Index of microcirculatory resistance and REDUCER

Full title:

Index of microcirculatory resistance evaluation in patient with Coronary Sinus Reducer Implantation for the treatment of chronic refractory Angina pectoris, the INROAD study

Principal Investigator information:

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Therapeutic area of interest

Chronic refractory Angina

Primary product

Coronary Sinus Reducer implantation

Area of study

Microcirculation resistance

Type of study

Investigator-driven, prospective, study

SUMMARY

INVESTIGATOR INFORMATION	
Name:	Matteo Tebaldi
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SHORT CONCEPT REQUIREMENTS		
☐	Study Title	Index of microcirculatory resistance evaluation in patients with Coronary Sinus Reducer Implantation for the treatment of chronic refractory Angina pectoris, the INROAD study
☐	Therapeutic Area of Research	Chronic refractory Angina
☐	Primary Product	Coronary Sinus Reducer implantation
☐	Area of Interest	Microcirculation resistance
☐	Type of Study	Investigator-driven, prospective, study. Patients undergoing coronary sinus reducer implantation (Reducer) for chronic refractory angina undergo evaluation of the index of microcirculatory resistance (IMR) at the time of implantation, and at 4 months follow-up.
☐	Resource Requested	Device, Pressure wire and funding
☐	Study Rationale/Goal	Evaluate if patients with refractory angina have a reduction of IMR after coronary sinus reducer implantation
☐	Primary Study Objectives/Endpoints	PRIMARY ENDPOINTS • Change in IMR value at 4 month follow-up

☐	Secondary Study Objectives/Endpoints	• Change in angina severity according to the Seattle Angina Questionnaire at 4 month • Change in Canadian Cardiovascular Society angina class by two or more classes at 4 month • Change in Beck depression inventory at 4 month • Change in CFR (coronary flow reserve) value at 4 month follow-up compare to baseline • Change in RRR (resistive reserve ratio) value at 4 month follow-up compare to baseline • Change in LVEDP (left ventricular end-diastolic pressure) value at 4 month follow-up compare to baseline • Change in Speckle tracking echocardiography (STE) value at 4 month follow-up compare to baseline • Change in coronary sinus PH, SP02, PCO2, HCO3,l actate value at 4 month follow-up compare to baseline
☐	Key Inclusion Criteria	- Age ≥ 18 years old - Chronic refractory angina refractory to medical and interventional therapies. - Ability to provide informed written consent - Life expectancy ≥1 year

☐	Efficacy Variables/Measures	Index of microcirculatory resistance (IMR)
☐	Safety Variables/Measures	NA
☐	Statistical & Analytical Plan	Continuous data will be tested for normal distribution with the Kolmogorov-Smirnov test. Normally distributed variables will be presented as mean±SD, otherwise will be presented as median and interquartile range (IQR). Normally distributed values will be compared by t test and 1-way ANOVA. Otherwise, the Mann-Whitney U and Kruskal-Wallis tests will be used. A linear mixed model will be used to quantify changes of study's variables over time while integrating the role of baseline and procedural characteristics. Categorical variables will be summarized in terms of number and percentages and will be compared by using two-sided Fisher's exact test. All statistical analyses will be performed by the Centro di Ricerca Clinica ed Epidemiologica of the University of Ferrara with STATA 13 (StataCorp, College Station, TX).
☐	Sample Size and Justification	Previous studies showed that the median value of IMR in patients with obstructive epicardial diseases was 22.9 ± 13.1, and about these patients 39% (15/38 patients) had an abnormal IMR (> 25).We estimate that 4 months after implantation of Reducer, patients will show values of IMR 20% lower as compared to those found before the procedure. To obtain a power of 90% (α=0.05) 17 patients must be enrolled.To

		cover dropouts, the sample size is arbitrarily increased to 20 patients.
☐	Number of Subjects	20
☐	Duration of Subjects on Study Drug	NA
☐	Preliminary Publication Plan	We estimate that 2 months will be necessary to achieve EC authorization and contract signature after the approval of the present purpose. We estimate that the enrolment will require 18 months if the study will be monocentric. The PI will try to involve at least one additional center to speed up the enrolment. After the enrollment of the last subject, we need 4 months to reach the primary endpoint evaluation. Then, we estimate that the primary endpoint findings will be available 22 months after the approval of the present purpose.

BACKGROUND

Refractory angina (RA) is a chronic condition (present for at least 3 months) of moderate-severe symptoms (Canadian class Cardiovascular Society [CCS] II-IV) due to coronary artery disease which cannot be adequately controlled by the combination of optimal medical therapy and coronary revascularization (percutaneous coronary intervention (PCI) or coronary artery by-pass graft (CABG). The angiographic anatomy of the patient with refractory angina can range from severe obstructive three-vessel coronary artery disease to the total absence of epicardial lesions [1]. Overall, about 92.3% of patients with refractory angina has a history of previous myocardial revascularization (PCI or CABG) [2].

Among patients revascularized for chronic stable angina, the prevalence of recurrent angina remains around 30-50% within the first year of a PCI and around 25% at 5 years from a CABG [3-4];in these patients the evolution towards refractory angina is about 5-10%[5-6], proportion destined to grow with the increase in life expectancy of coronary heart disease patients [7,8]. Despite many of the patients are labeled as having coronary artery disease "end-stage"[1,8] their overall prognosis is favorable, with a 9-year survival of 77.6% [2]. However, the clinical impact in terms of quality of life, re-hospitalization and socio-health costs is extremely negative. In this context, the therapeutic goals are primarily the management of the symptom and improvement the patient's quality of life. The unpaid therapeutic demand of these patients has brought out a large number of medical and interventional treatments, including: the use of ivabradine, ranolazine, external counterpulsation, spinal cord stimulation [9]. Among these, the coronary sinus reduction system (REDUCER) has also been introduced in the recent ESC guidelines[9], as one of the options that may be considered to ameliorate symptoms of debilitating angina refractory to optimal medical and revascularization strategies.

The coronary sinus Reducer device

The coronary sinus Reducer device is a stainless-steel mesh designed to create a focal narrowing in the lumen of the coronary sinus (CS) to generate a pressure gradient across it. The narrowing within the CS, and the pressure gradient across the device are established 4–6 weeks after implantation, when the metal mesh should be covered by tissue in growth [10.].

Numerous clinical studies and registries have been carried out and they proved both the efficacy and safety in the use of REDUCER. The most representative study, as it is randomized, is certainly COSIRA. This is a randomized, double-blind, sham-controlled, multi-centre clinical trial (COSIRA) [11] that enrolled 104 patients with severe refractory angina (CCS class III–IV), and objective evidence of myocardial ischaemia. Narrowing of the CS was associated with a greater angina relief than sham procedure (>_1 CCS grade improvement in 71% vs. 42%, (P= 0.003); >_2 CCS grades improvement in 35% vs. 15%, (P= 0.024). Quality-of-life as measured by the Seattle Angina Questionnaire was significantly improved in the treatment group compared to the sham control group (17.6 vs. 7.6 points improvement, respectively, P= 0.03). There was no difference in the rate of adverse events observed between the treatment and the sham control groups. It has recently been demonstrated that the advantages and safety in the Reducer patients are maintained even after a follow-up of 2 years. [12] A cost-economic analysis has also shown that in patients with RA, Reducer device decreases healthcare resource use and related costs.[13.].

REDUCER: mechanism of action

The physiological mechanism that are supposed to be behind the antianginal effect of coronary sinus intervention are essentially two:

1) Redistribution of coronary flow from the subepicardium to the subendocardium.

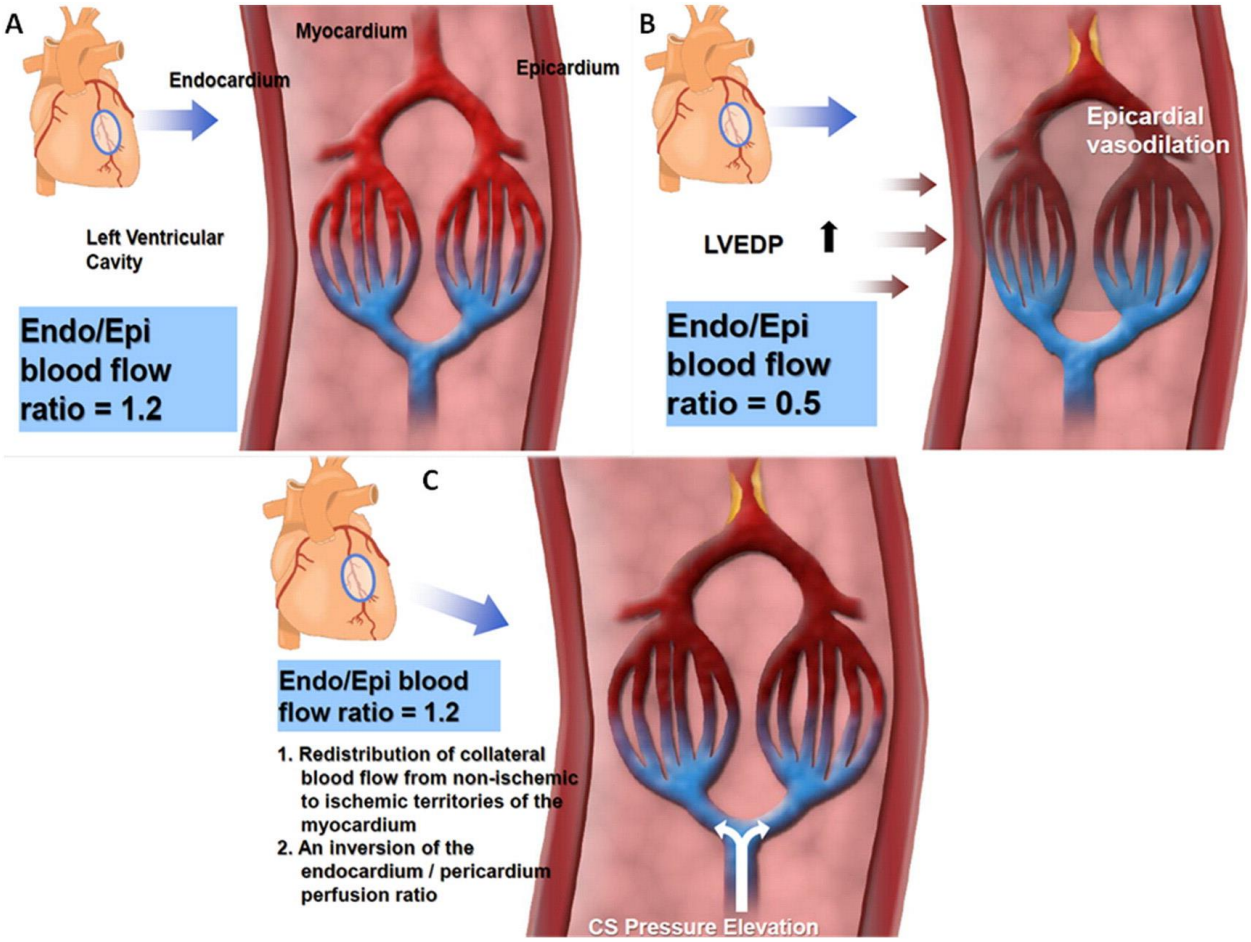
The suggested anti-ischemic effect of the CS Reducer is based on the hypothesis described by Camici et al. [14-15], according to which, in a normal heart, during exercise there is a sympathetically mediated constriction of subepicardial vessels which leads to a preferential blood flow towards the subendocardial capillaries. In patients with obstructive CAD this physiologic compensatory mechanism is dysfunctional [14-15]. In addition, in the presence of ischemia, impaired contractility and elevated left ventricle end-diastolic pressure (LVEDP) exert an external pressure on the subendocardial capillaries which further increases the resistance to flow to the subendocardium, leading to a vicious cycle of worsening subendocardial ischemia. Elevated CS pressure causing backwards pressure elevation in the venules and capillaries will result in a slight dilatation of the capillaries' diameter and a significant reduction of the resistance to flow. As a consequence of the reduction in subendocardial capillary resistance, the normal subepicardial to subendocardial blood flow ratio will be restored [16]. The result of this process is

an enhancement of blood flow to the ischaemic subendocardial layers of the myocardium, which will improve contraction, reduce LVEDP and lead to symptoms relief.

2) Coronary neoangiogenesis. The histological analysis of myocardial preparations of swine treated with Reducer, he demonstrated, 12 weeks after implantation, transmural intramyocardial neoangiogenesis.

In both cases, the *primum movens* of the Reducer's therapeutic mechanism is attributable to the increase in venous pressure due to narrowing of the coronary sinus.

Figure 1 Supposed mechanism of action of the Reducer [14]



Index of microcirculatory resistance (IMR)

Different techniques for measurement of Microcirculation have been introduced [17]. The most accurate and reproducible index is the index of microcirculatory resistance (IMR) first described in 2003 [18]. IMR is a coronary guidewire-based measure of coronary microvascular function. IMR provides information on microvascular dysfunction that could be informative both in stable patients and also in patients with acute or recent myocardial infarction. The IMR is calculated by multiplying the distal coronary pressure by the mean transit time of a 3 ml bolus of saline at room temperature during coronary hyperaemia induced by intravenous adenosine. Normal values are usually reported as ≤25. IMR is not significantly affected by the presence of an epicardial vessel stenosis and changes in heart rate, blood pressure, and contractility.
It has been supposed that an increased pression in the coronary venous system could determine a reduction of subendocardium ischemia and, consequently, angina symptoms.[10]. In this setting, the IMR value should not only be considered as an index of microcirculation dysfunction, but also as a marker of the effectiveness of the Reducer treatment. Therefore, not only patients with IMR> 25 will be selected, as the symptoms of these patients who on average have an IMR value of 22 are present even with values lower than that of the prespecified cut-off.

FIGURE 2 IMR computation

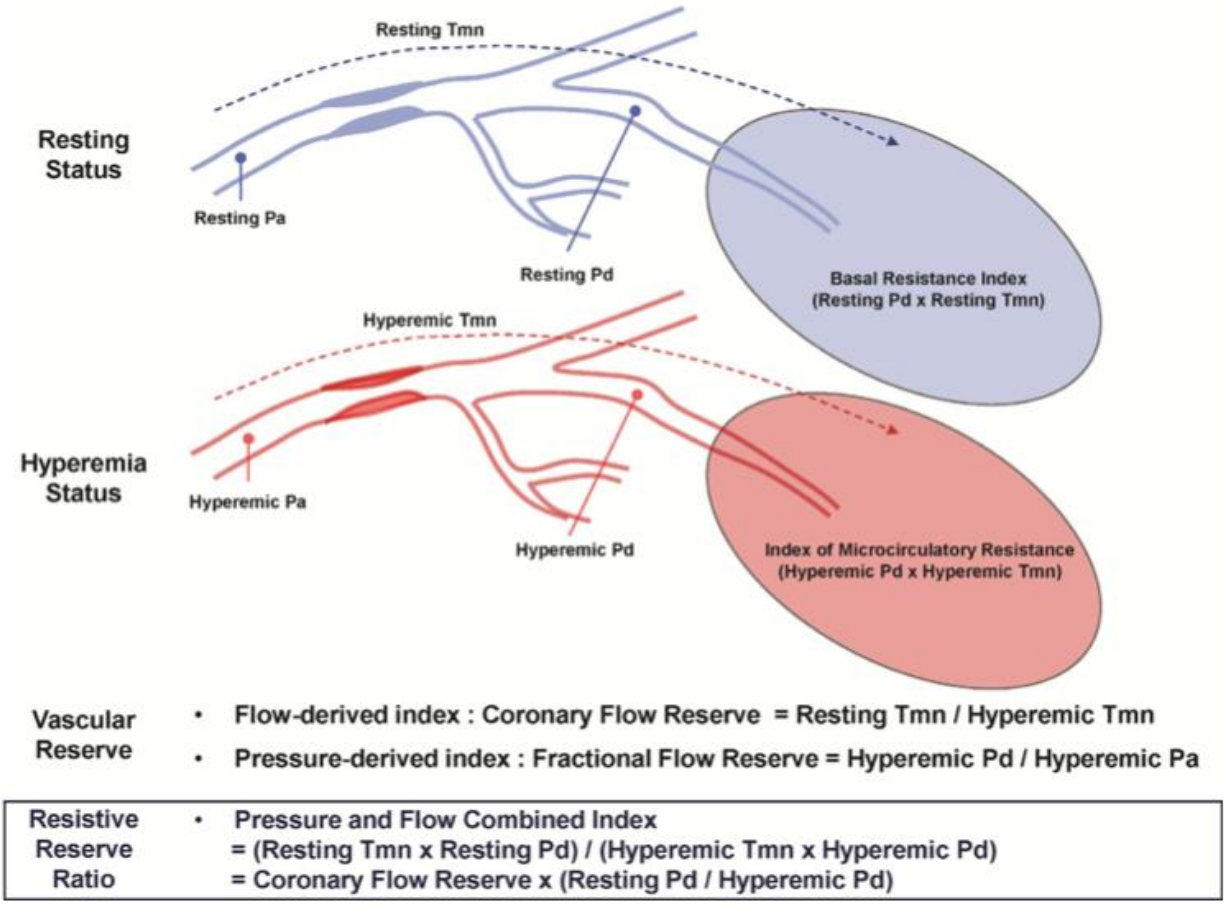
Coronary flow reserve (CFR)

CFR is defined as hyperemic coronary flow divided by resting flow and can be measured invasively in the catheterization laboratory with a cut-off of normality ≥ 2.0. CFR was developed first as an invasive method to interrogate intermediate epicardial coronary lesions. Because it interrogates the entire coronary circulation, both the epicardial vessel and the microvasculature, CFR has been applied more recently as a technique for diagnosing microvascular dysfunction in patients without obstructive epicardial coronary disease. Because CFR incorporates resting flow in its definition, it has more variability and less reproducibility compared with IMR.

Resistive Reserve ratio (RRR)

Resistive reserve ratio (RRR) is a thermodilution-based index which integrates both coronary flow and pressure. It represents the vasodilatory capacity of interrogated vessels including both epicardial coronary artery and microvascular circulation (Figure 3). RRR was calculated as the ratio between resting and hyperemic distal coronary pressure ([resting Tmn/hyperemic Tmn] × [resting Pd/ hyperemic Pd]); which can therefore be simplified as the relationship between CFR x [resting Pd/ hyperemic Pd]. Cut-off values is > 3.5.[19]

Figure 3_ Resistive reserve ratio (RRR) physiological explanation



Venous coronary sinus blood gas

Previous studies have shown how tissue acidosis in the myocardium is an important cause of contractile failure during ischemia. [20] The demonstration of a shift towards a more acid pH in the coronary sinus blood, a drop in coronary sinus oxygen saturation and a change in myocardia lactate extraction ratio have all been used as metabolic markers of myocardial ischaemia. [21]. In the same way, a coronary sinus pH decrease associated with an increase in saturation and a decrease in myocardia lactate can be considered as indicators of improvement in the ischemic burden.

	Normal range
PH	7.33-7.44
PC02 (KPA)	5.0-6.4
PO2 (KPA)	5.3
HC03 (mmol)	22-28
S02 (%)	72-75
Lactate (mmol/L)	0.5-2.2

Speckle tracking echocardiography (STE)

Speckle tracking echocardiography (STE) provides non-Doppler, relatively angle-independent measurement of myocardial deformation of the LV (left ventricular), right ventricular (RV), and atrial walls. In particular it allows the semi-automated quantification of myocardial strain and strain rate (SR) in the 3 main spatial directions (longitudinal, radial, and circumferential) and a concomitant evaluation of LV mechanics in terms of rotation and torsion. STE is particularly suited for the estimation of systolic function, can manifest in more than 1 direction before the development of abnormalities on conventional measures of cardiac performance, such as the LV-EF. Current software measure longitudinal strains of individual LV myocardial segments and calculate a global longitudinal strain (GLS) by averaging local strains. In addition, peak systolic longitudinal myocardial strains measured throughout the myocardium for each LV apical view can be reported spatially, from base to apex and circumferentially, in a polar diagram using a color-coded parametric representation this facilitates rapid visual assessment of myocardial deformation of the entire LV. [22] However, GLS is a parameter load -dependent. The analysis of myocardial work by LV pressure strain analysis incorporates LV pressure analysis providing incremental information compared to the load dependent measurements as GLS and EF. With dedicated software it is possible to calculate the following parameters: constructive work (positive work performed by normal, vital contracting segments); wasted work (work that does not contributes to LV ejection as in case of dyssynchrony) and myocardial work efficiency as the ratio between constructive and the sum of constructive and wasted work.

Left ventricular end diastolic pressure (LVEDP)

The left ventricular end-diastolic pressure (LVEDP) is a haemodynamic parameter that is routinely obtained during cardiac catheterization and is a measure of intravascular volume status. It has been shown that its value correlates with the prognosis of patients with acute coronary syndrome.[23]A 6 F pig tail catheter was placed in the LV using the radial percutaneous approach. The pressure was balanced and calibrated with the external pressure transducer positioned at the mid axillary level. All the recordings were performed before the injection of the contrast agent. The LVEDP is measure 50 ms after the beginning of the QRS complex, usually coinciding with the R wave. The normal LVEDP cut-off is 15 mmHg.

HYPOTHESIS

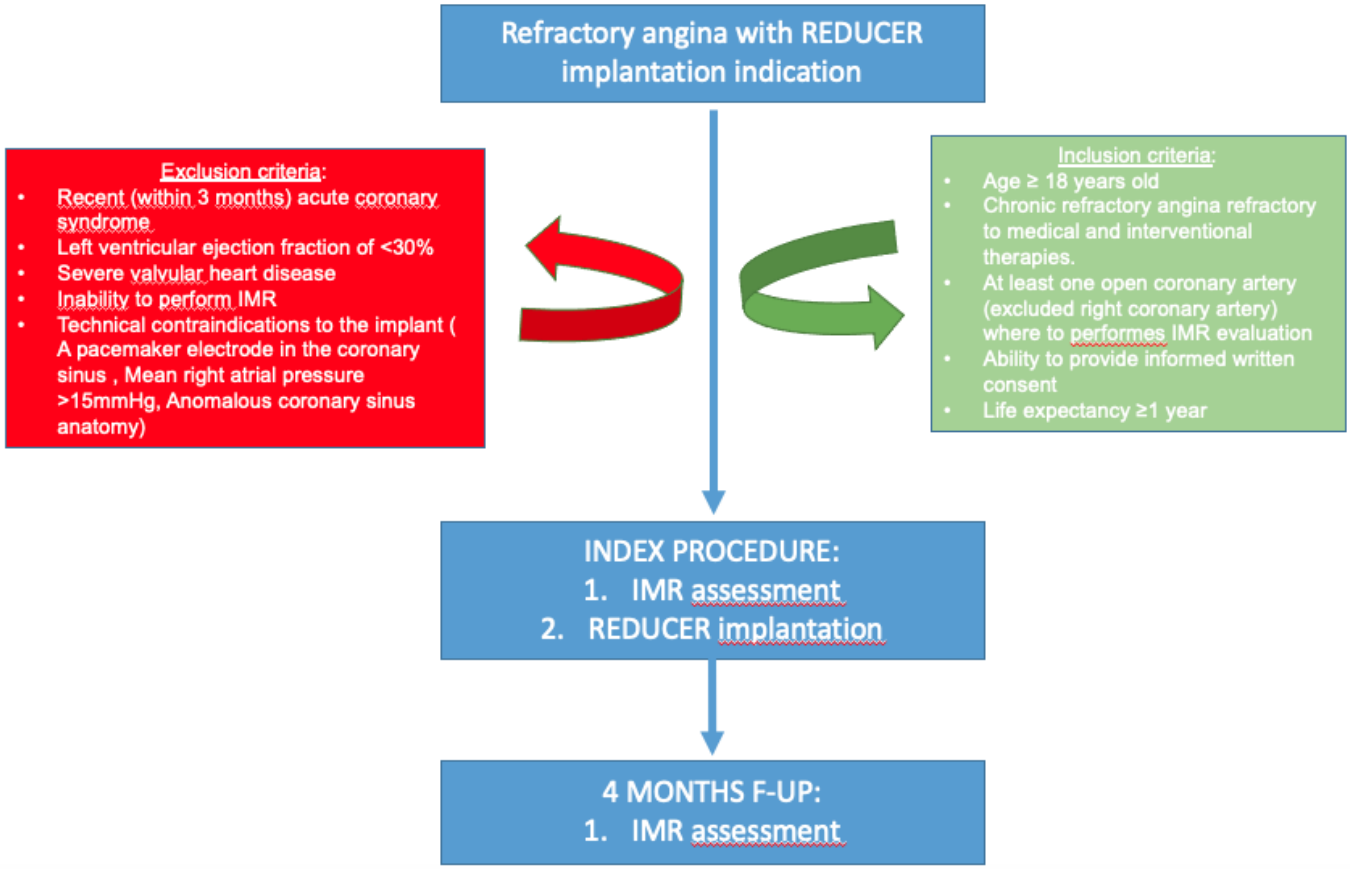
It has been supposed that an increased pression in the coronary venous system could determine a vasodilatation of the arterioles, reducing resistances in the subendocardium vessels and favoring a blood redistribution from subepicardial layers to subendocardium, with a reduction of subendocardium ischemia and, consequently, angina symptoms .[10].

Nevertheless, this mechanism of action is theoretical and has never been objectively tested. The evaluation of microcirculatory resistance by IMR before and after REDUCER implantation could be the most effective way to confirm this hypothesis.

STUDY DESIGN

This is an investigator-driven, prospective, study. Patients undergoing coronary sinus reducer implantation (Reducer) for chronic refractory angina, that meet the inclusion criteria and have provided informed consent, will undergo evaluation of the index of microcirculation resistance (IMR) before the implantation, and after 4±1 months (see figure 3).

Figure 3. Study flow-chart



ENDPOINTS OF THE STUDY

Primary endpoint

- Significant Change (≥ 20%) in IMR value at 4 month follow-up as compared to baseline value

Secondary endpoints

- Change in angina severity according to the Seattle Angina Questionnaire at 4 month
- Change in Canadian Cardiovascular Society angina class by two or more classes at 4 month
- Change in Beck depression inventory at 4 month
- Change in CFR (coronary flow reserve) value at 4 month follow-up compare to baseline
- Change in RRR (resistive reserve ratio) value at 4 month follow-up compare to baseline
- Change in LVEDP (left ventricular end-diastolic pressure) value at 4 month follow-up compare to baseline
- Change in Speckle tracking echocardiography (STE) value at 4 month follow-up compare to baseline
- Change in coronary sinus PH, SP02, PCO2, HCO3,lactate value at 4 month follow-up compare to baseline

RATIONAL FOR STUDY DESIGN AND SELECTED ENDPOINTS

Strengths of the study design and selected endpoint

- The IMR evaluation being a parameter that takes into account only the microcirculation resistances, and can be quickly evaluated in the cath-lab , allows to evaluate if the decrease of the microcirculation resistances are one of the mechanisms underlying the Reducer functioning.

INCLUSION CRITERIA

- Age ≥ 18 years old
- Chronic refractory angina refractory to medical and interventional therapies.
- At least one open coronary artery (excluded right coronary artery) where to performs IMR evaluation
- Ability to provide informed written consent
- Life expectancy ≥1 year

EXCLUSION CRITERIA

- Recent (within 3 months) acute coronary syndrome
- Left ventricular ejection fraction of <30%
- Severe valvular heart disease
- Inability to perform IMR
- Technical contraindications to the implant (pacemaker electrode in the coronary sinus, mean right atrial pressure >15mmHg, anomalous coronary sinus anatomy)

STUDY CONDUCT

Enrollment

Eligible patients must sign informed consent prior to undergoing any study-specific procedures and At inclusion in the study, the following routine parameters will be captured: physical examination, relevant medical and cardiac history, concomitant medications, anginal status, respiratory status, laboratory data including blood cell count, haemoglobin, renal function, liver function, lipid profile.

Informed consent

All potential subjects must be consented prior to undergoing any study-specific procedures. Once the subject's general eligibility for the study is met, the background of the proposed study and the benefits and risks of the procedures and study must be explained to the subject prior to obtain informed consent. Only those subjects who sign the Ethics Committee (EC) approved informed consent form prior to any study-specific procedures are candidates for actual enrolment in the study. Failure to provide written informed consent renders the subject ineligible for the study. If the subject is unable to consent, a written consent from a legally acceptable representative will be accepted to facilitate the participation in this clinical study. The legal representative may provide written consent – if approved by local IRB regulations – on behalf of the subject only after he or she is fully informed about the study. In case the subject is unable to read, an impartial witness (this can be any person who is independent of this study) must be present during the entire informed consent discussion. Once the subject gives oral consent, the witness must sign and personally date the consent form. This will confirm that the information in this informed consent and any further information provided by the investigator was explained to and understood by the subject and that consent was freely given. In case of the subject's verbal consent or in case a legal representative consent on behalf of the subject, the subject will be asked to sign the consent form himself/herself when the investigator decides the subject is able to understand the contents of the subject information sheet and is able to sign and date the informed consent form. The investigator and/or designee must also clearly document the process of obtaining informed consent in the subject's source documents. The voluntary process of obtaining informed consent confirms the subject's willingness to participate in the study. It is the investigator's responsibility

to ensure that the informed consent process is performed in accordance with ICH-GCP, EC requirements and country specific regulations.

Index procedure

Day 1

The patient is admitted to the cardiology ward, and routine assessment procedures are performed for patients with CCS: blood samples, Seattle Angina Questionnaire, Beck depression inventory, Canadian Cardiovascular Society angina class and Speckle tracking echocardiography.

Day 2

The patient undergoes a coronary study and Reducer implantation by following the standard procedure:

1) A 6 F introducer is placed in the radial artery
2) A 9 F introducer is placed in the right jugular vein by using ultrasound guidance
3) Coronary angiography is performed using a diagnostic catheter (Judkins right) for the right coronary artery and a procedural catheter (EBU 3.75) for the left coronary system
4) left ventricular end diastolic pressure (LVEDP) evaluation was performed by placing a 6 F pig tail in the left ventricle.
5) assessment of the complete functional evaluation: index of microcirculatory resistance (IMR), coronary flow reserve (CFR), and resistive reserve ratio (RRR) evaluation by using the Pressure wire X (Abbott), in the left coronary system as previously described [18]
6) We proceed with the implantation, through the right jugular vein, of the coronary sinus reduction system (REDUCER) as per standard procedure [11] Performing a Venous coronary sinus blood gas before implantation

Day 3

The patient will be discharged from the cardiology ward. At hospital discharge, an assessment of the Serious Adverse Events (SAE) and Adverse device effect (ADE) will be recorded, and an EKG will be performed

2-month follow-up visit

Patients will be followed from hospital discharge for up to 12 months. At 2-month, patients will receive a clinical visit to obtain information regarding clinical status, cardiovascular drug use and compliance, hospitalizations, serious adverse events and to collect study blood samples. Seattle Angina Questionnaire, Beck depression inventory, Canadian Cardiovascular Society angina class, will be assessed at clinical visit.

4-months hospital admission to repeat IMR evaluation

After 4 month the patient will be hospitalized to perform functional evaluation by IMR (Primary endpoint).

The patient is admitted to the cardiology ward, and routine assessment procedures are performed for patients with CCS: blood samples, Seattle Angina Questionnaire, Beck depression inventory, Canadian Cardiovascular Society angina class and and Speckle tracking echocardiography

The patient undergoes a coronary study following the standard procedure:

1) A 6 F introducer is placed in the radial artery
2) A 6 F introducer is placed in right jugular vein by using ultrasound guidance
3) Coronary angiography is performed using a diagnostic catheter (Judkins right) for the right coronary artery and a procedural catheter (EBU 3.75) for the left coronary system
4) We will performe left ventricular end diastolic pressure (LVEDP) evaluation by placing a 6 F pig tail in the left ventricle
5) We will performe the complete functional evaluation: index of microcirculatory resistance (IMR), coronary flow reserve (CFR), and resistive reserve ratio (RRR) evaluation by using the Pressure wire X (Abbott), in the left coronary system as previously described [18]
6) We will performe a venous coronary sinus blood gas by placing a 6 F multipurpose catheter.

The patient will be discharged from the cardiology ward. At hospital discharge, an assessment of the Serious Adverse Events (SAE) and Adverse device effect (ADE) will be recorded, and an EKG will be performed

6-months follow-up visit

At 6-month, patients will receive a clinical visit to obtain information regarding clinical status, cardiovascular drug use and compliance, hospitalizations, serious adverse events and to collect study blood samples. Seattle Angina Questionnaire, Beck depression inventory, Canadian Cardiovascular Society angina class, will be assessed at clinical visit

12-months follow-up visit

At 12-month, patients will receive a clinical visit to obtain information regarding clinical status, cardiovascular drug use and compliance, hospitalizations, serious adverse events and to collect study blood samples. Seattle Angina Questionnaire, Beck depression inventory, Canadian Cardiovascular Society angina class, will be assessed at clinical visit

	Screening	Procedure	Hospital Discharge	Two months (visit)	Four months (Hospitalization)	Six months (visit)	Twelve months (visit)
Informed consent	x						
Medical history	x			x	x	x	x
Physical exam	x			x	x	x	X
Listing of current medications	x			x	x	X	x
Blood work	x		x		x		
EKG	x		x	x	x	x	X
CCS assesment	x			x	x	X	x
Speckle tracking echocardiography	x				x		
SAQ	x			x	x	x	X
Beck depression inventory	x			x	x	X	x
Complete functional assessment (IMR,CFR,RRR)		x			x		
LVEDP evaluation		x			x		
Venous coronary sinus blood gas		x			x		
Reducer Implantation		x					
Adverse device effect (ADE)		x			x		
Adverse event (AE)			x	x	x	x	x

Concomitant and post-study treatment(s)

Interventional procedures and cardiovascular drugs will be prescribed and performed as recommended by current guidelines and patient's status.

Data collection

All required data will be accurately recorded by study staff in the case report form (CRF) of the study. The database will be located in the Cardiology Unit of the Azienda Ospedaliera Universitaria di Ferrara under the responsibility of the principal investigator.

Withdrawal from study

After entering into the study, the patients are asked to complete scheduled follow-up visits (2 month) and coronary angiography at 4 months. Patients will be exempt from follow-up only if they withdraw their consent. Every patient should be encouraged to remain in the study until he/she has performed the coronary angiography at 4-month follow-up. Possible reasons for premature discontinuation may include, but are not limited to, the following:

- Withdrawal of consent: Patient decides to withdraw from the study. The decision must be an independent decision that is documented in the patient study files.
- Physician discretion: The investigator may choose to withdraw a patient from the study if he/she considers follow-up too burdensome for the patient.
- Lost to follow-up: All patients should be encouraged to return for the follow-up visit and the 4 months hospedalization, and to provide appropriate contact information to accommodate completion of required telephone follow-ups.

The investigator will attempt to contact the patient at follow-up visit, independent of any missed follow-ups. The investigator should make 3 documented attempts per required follow-up visit. Patients who have discontinued the trial prematurely will not be replaced.

MAIN DEFINITIONS

Chronic refractory angina

Refractory angina (RA) is conventionally defined as a chronic condition (≥3 months in duration) characterised by angina in the setting of coronary artery disease (CAD), which cannot be controlled by a combination of optimal medical therapy, angioplasty or bypass surgery, and where reversible myocardial ischaemia has been clinically established to be the cause of the symptoms [24]

Angina severity according to Canadian cardiovascular Society (CCS)

The Canadian Cardiovascular Society classification is still widely used as a grading system for angina to quantify the threshold at which symptoms occur in relation to physical activities (Table 1) [9]

Table 1 Angina Severity

Grade	Description of angina severity	
I	Angina only with strenuous exertion	Presence of angina during strenuous, rapid, or prolonged ordinary activity (walking or climbing the stairs).
II	Angina with moderate exertion	Slight limitation of ordinary activities when they are performed rapidly, after meals, in cold, in wind, under emotional stress, or during the first few hours after waking up, but also walking uphill, climbing more than one flight of ordinary stairs at a normal pace, and in normal conditions.
III	Angina with mild exertion	Having difficulties walking one or two blocks, or climbing one flight of stairs, at normal pace and conditions.
IV	Angina at rest	No exertion needed to trigger angina.

The Seattle Angina Questionnaire (SAQ)

The Seattle Angina Questionnaire, a 19-item self-administered questionnaire measuring five dimensions of coronary artery disease: physical 11 limitation, angina stability, angina1 frequency, treatment satisfaction and disease perception[25]. Each scale is transformed to a score of 0 to 100, where higher scores indicate better function. The self-administered SAQ to be completed by study patients will be analyzed with the statistical software provided by Cardiovascular Outcomes, Inc.

Beck depression inventory

The Beck Depression Inventory (BDI) is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression [26]. Each question has a set of at least four possible answer choices, ranging in intensity. When the test is scored, a value of 0 to 3 is assigned for each answer (0= I do not feel sad, I=feel sad, 2 =I am sad all the time and I can't snap out of it, 3= I am so sad or unhappy than I can't stand it) and then the total score is compared to a key to determine the depression's severity (0-9= indicates minimal depression, 10-18= indicates mild depression, 19-29= indicates moderate depression, 30-36= indicates severe depression).

STATISTICAL ANALYSIS

Continuous data will be tested for normal distribution with the Kolmogorov-Smirnov test. Normally distributed variables will be presented as mean±SD, otherwise will be presented as median and interquartile range (IQR). Normally distributed values will be compared by t test and 1-way ANOVA. Otherwise, the Mann-Whitney U and Kruskal-Wallis tests will be used. A linear mixed model will be used to quantify changes of study's variables over time while integrating the role of baseline and procedural characteristics. Categorical variables were summarized in terms of number and percentages and were compared by using two-sided Fisher's exact test. All statistical analyses will be performed by the Centro di Ricerca Clinica ed Epidemiologica of the University of Ferrara with STATA 13 (StataCorp, College Station, TX).

Sample size calculation

Previous studies showed that the median value of IMR in patients with obstructive epicardial diseases was 22.9 ± 13.1, and about these patients at least 39% (15/38 patients) had an abnormal IMR value (> 25). We estimate that 4 months after implantation of Reducer, patients will show values of IMR 20% lower as compared to those found before the procedure. To obtain a power of 90% (α=0.05) 17 patients must be enrolled. To cover dropouts, the sample size is arbitrarily increased to 20 patients.

SAFETY

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

Definition of Adverse Device Effect

Adverse event related to the use of a medical device.
Note 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation or any malfunction of the medical device;
Note 2: This includes any event that is a result of a use error or intentional misuse.

Definition of Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects whether or not related to the investigational device. The term AE is used to include both serious and non-serious AEs.

Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to local Authorities.

Recording of adverse events

Any event meeting the above-mentioned definitions must be reported to the sponsor on an adverse event form. Adverse events must be documented on an "Adverse event" form according to the general instructions for completion available in the e-CRF. The investigator must document the date of onset, the measures taken, the outcome and the date of recovery or stabilization of the event. He / she must assess the event in terms of intensity, causality and seriousness, and whenever possible should establish a medical diagnosis and enter it in the e-CRF. The investigator must ensure that the follow-up of the patient is appropriate to the nature of the event, and that it continues until resolution. He / she must immediately inform the sponsor of any secondary worsening of the event. Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an adverse event already reported must be written up in a new complete evaluation of the event documented on the "Adverse event" form of the e-CRF. If the adverse event has not resolved or stabilised at the patient's final visit in the study, the patient must be followed up suitably and any information on the outcome of the event will be noted on the "Adverse event" form of the e-CRF. As far as possible, a follow-up visit will be organised to collect the information relating to the outcome of the event. If necessary, the information will be collected afterwards, up to resolution or stabilisation of the patient’s clinical status. If the follow-up of the patient is not done by the investigator him / herself (hospitalisation, follow-up by a specialist or the patient's general practitioner, …), the investigator will do everything possible to establish / maintain contact with the person / department in charge of the follow-up of the patient, so as to collect additional information and report it on the "Adverse event" form of the e-CRF.

Reporting of serious adverse events

The Sponsor/Investigator is responsible for meeting all regulatory safety reporting requirements and obligations. This includes expedited reporting off all serious, unexpected and possibly study drug- related SAEs (SUSAR) from the study to the Regulatory Authority and IEC/IRB, as required. The investigators are instructed to interview each patient carefully at each study visit to determine if an adverse event may have occurred. If an event fulfils the criteria for SAE, then this shall be reported in the eCRF within 24 hours of the clinic study staff having become aware of this, including their judgement regarding causal relationship of the event to the trial. The Investigator must inform the local Authorities and Ethical Committees of any serious adverse events as per local requirements.

ETHICAL AND REGULATORY REQUIREMENTS

EC approval

According to the local regulations, the investigator must have all necessary approvals, including written approval from the EC of the clinical site or other accepted EC prior to enrolling patients in the study. A copy of the written approval must be provided to Sponsor and should include the following:

- Statement of EC approval for the proposed study at the clinical site
- Date the study was approved and the duration of the approval
- Listing of any conditions attached to the approval
- Identification of the approved Primary Investigator
- Signature of the EC chairperson
- Acknowledgement of the Co-Investigators
- EC approval of the informed consent form (if applicable)
- EC approval of the final protocol (if applicable).

Any substantial amendments to the protocol, as well as associated consent form changes, will be submitted to the EC and written approval obtained prior to implementation. Minor changes which do not affect the subject's safety will be subject to notification. Serious Adverse Event (SAE) reports will be submitted to the EC as requested by the Sponsor, EC and/or local regulations. Annual and final reports will be provided to the EC as required.

Informed consent

Study subjects must provide written informed consent using an EC-approved informed consent form. The study must be explained to the study subjects in lay language. The investigator, or representative, must be available to answer all of the study subject's study-related questions. Study subjects will be assured that they may withdraw from the study at any time for any reason and receive alternative conventional therapy as indicated.

Protocol deviation

The investigator will report all protocol deviations to the Sponsor and will inform the EC according to the EC requirement.

Audits

If audits are initiated by the Sponsor (or its designee) or national/international regulatory authorities, the investigator allows access to the original medical records and provides all requested information. If audits are initiated by a regulatory authority, the investigator will immediately notify the Sponsor.

STUDY MANAGEMENT AND ORGANIZATION

Compliance to Standards and Regulations

The protocol, informed consent form and other study-related documents will be submitted to the Ethics Committee (EC) / Institutional Review Board (IRB) and competent authorities, if applicable. The study will be performed in accordance with the Declaration of Helsinki and Good Clinical Practices (GCP). The trial will only start at a clinical site after written approval of the study has been obtained from the appropriate national EC/IRB and the competent authorities.

SPONSOR AND COMMITTEE

- SPONSOR: Consorzio Futuro e Ricerca (CFR)
- STEERING COMMITTEE: it is responsible of the overall management of the study at the highest level. The Steering Committee of the present study is Matteo Tebaldi, Gianluca Campo, Simone Biscaglia.
- DATA SAFETY MONITORING BOARD (DSMB): Ennio Scollo, Andrea Marrone, Federico Gibiino
- DATA MANAGEMENT: Data management will be conducted by the research staff of the Cardiovascular Institute of the Azienda Ospedaliera Universitaria di Ferrara, via Aldo Moro 8, Cona (FE), Italy under the supervision of Veronica Lodolini, Martina Viola, Chiara Manzalini, Elisa Mosele.

OWNERSHIP OF DATA AND USE OF THE STUDY RESULTS

The sponsor has ownership of all data and results collected during this study. The sponsor guarantees full publication rights of the study to the Study Principal Investigator.

PUBLICATIONS

All study presentations and/or publication of the results will be based on clean, checked and validated data in order to ensure the accuracy of the results. Publication of the main findings of this study will be authored based on the contributions of the individuals to the overall study. All the trial participants (Investigators and committee members) make a prior delegation of responsibility for primary presentation and/or primary publication of the results to the Study Principal Investigator.

REFERENCES

1. Jolicoeur EM, Cartier R, Henry TD, et al. Patients with coronary artery disease unsuitable for revascularization: definition, general principles, and a classification. Can J Cardiol 2012;28(2 Suppl):S50-9
2. Henry TD, Satran D, Hodges JS, et al. Long-term survival in patients with refractory angina. Eur Heart J 2013;34:2683-8.
3. Hemingway H, Crook AM, Feder G, et al. Underuse of coronary revascularization procedures in patients considered appropriate candidates for revascularization. N Engl J Med 2001;344:645-54.
4. Abdallah MS, Wang K, Magnuson EA, et al.; SYNTAX Trial Investigators. Quality of life after surgery or DES in patients with 3-vessel or left main disease. J Am Coll Cardiol 2017;69:2039-50
5. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina: report from the ESC Joint Study Group on the Treatment of Refractory Angina. Eur Heart J 2002;23:355-70
6. Bernstein SJ, Brorsson B, Aberg T, Emanuelsson H, Brook RH, Werkö L Appropriateness of referral of coronary angiography patients in Sweden. Heart 1999;81:470-7
7. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics – 2017 update: a report from the American Heart Association. Circulation 2017;135:e146-603
8. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.
9. Jnuuti J., Wijns W., Saraste A., et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European Heart Journal (2020) 41, 407-477
10. Maayan Konigstein, Francesco Giannini, Shmuel Banai" The Reducer device in patients with angina pectoris: mechanisms, indications, and perspectives" Eur Heart J. 2018;39:925–933
11. Stefan Verheye 1, E Marc Jolicœur, Miles W Behan, et al. "Efficacy of a device to narrow the coronary sinus in refractory angina" N Engl J Med 2015 Feb 5;372(6):519-27

12. Francesco Ponticelli, Giorgos Tzanis, Guglielmo Gallone, et al. “Safety and efficacy of Coronary Sinus Reducer implantation at 2-year follow-up” Int J Cardiol 2019 Oct 1;292:87-90
13. Guglielmo Gallone, Patrizio Armeni , Stefan Verheye, et al.” Cost-effectiveness of the coronary sinus Reducer and its impact on the healthcare burden of refractory angina patients” Eur Heart J Qual Care Clin Outcomes 2020 Jan 1;6(1):32-40
14. Ielasi A, Todaro MC, Grigis G., et al. “Coronary Sinus Reducer system™: A n therapeutic option in refractory angina patients unsuitable for revascularization” International Journal of Cardiology 209 (2016) 122–130
15. P.G. Camici, F. Crea, Coronary microvascular dysfunction, N. Engl. J. Med. 356 (2007) 830–840.
16. A. Ido, N. Hasebe, H. Matsuhashi, K. Kikuchi, Coronary sinus occlusion enhances coronary collateral flow and reduces subendocardial ischemia, Am. J. Physiol. Heart Circ. Physiol. 280 (2001) H1361–H1367
17. Fearon W., Kobayashi Y., “Invasive Assessment of the Coronary Microvasculature The Index of Microcirculatory Resistance” Circ Cardiovasc Interv. 2017;10:e005361”
18. Fearon WF, Balsam LB, Farouque HM, et al. “Novel index for invasively assessing the coronary microcirculation”. Circulation. 2003;107:3129–3132
19. Lee SH, Lee JM, Park J, Prognostic Implications of Resistive Reserve Ratio in Patients With Coronary Artery Disease J Am Heart Assoc. 2020 Apr 21;9(8):e015846
20. S M Cobbe, P A Poole-Wilson Continuous coronary sinus and arterial pH monitoring during pacing-induced ischaemia in coronary artery disease Br Heart J1982 Apr;47(4):369-74
21. G M Rosano, J C Kaski, S Arie, W I Pereira, et al. “Failure to demonstrate myocardial ischaemia in patients with angina and normal coronary arteries. Evaluation by continuous coronary sinus pH monitoring and lactate metabolism” Eur Heart J1996 Aug;17(8):1175-80
22. D'Andrea A, Nistri S. ,Castaldo F, et al “ The relationship between early left ventricular myocardial alterations and reduced coronary !ow reserve in non-insulin-dependent diabetic patients with microvascular angina “International Journal of Cardiology 154 (2012) 250–255

23. Leistner DM, Dietrich S., Erbay A et al. “Association of left ventricular end-diastolic pressure with mortality in patients undergoing percutaneous coronary intervention for acute coronary syndromes” Catheter Cardiovasc Interv. 2020;1–8.
24. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina; report from the ESC Joint Study Group on the Treatment of Refractory Angina. Eur Heart J 2002;**23**:355–70. DOI: 10.1053/euhj.2001.2706; PMID: 11846493
25. 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 Coli Cardiol 1995;25:333-41)
26. Beck, A.T., Ward, C. H., Mendelson, et al. (1961) An inventory for measuring depression. Archives of General Psychiatry, 4, 561-571