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Contemporary and future invasive coronary vasomotor function testing and treatment in patients with ischaemia with no obstructive coronary arteries

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In the current review, we emphasize the importance of diagnostics and therapy in patients with ischaemia with no obstructive coronary arteries (INOCA). The importance of the diagnostic coronary function test (CFT) procedure is described, including future components including angiography-derived physiology and invasive continuous thermodilution. Furthermore, the main components of treatment are discussed. Future directions include the national registration ensuring a high quality of INOCA care, besides a potential source to improve our understanding of pathophysiology in the various phenotypes of coronary vascular dysfunction, the diagnostic CFT procedure, and treatment.

Introduction

Angina pectoris is the most common symptom of myocardial ischaemia, and affects more than 100 million people worldwide.[1] Approximately half of all patients who undergo coronary angiography for ischaemic symptoms do not have obstructive coronary artery disease (CAD).[2] Underlying coronary-related mechanisms other than obstructive atherosclerotic CAD for myocardial ischaemia include myocardial bridging, primary metabolic abnormalities, inflammation, systemic inflammatory and autoimmune disease, platelet and coagulation disorders, and vasomotor dysfunction. In the majority of these patients with ischaemia with no obstructive coronary arteries (INOCA), the symptoms or ischaemia are caused by underlying coronary vascular dysfunction (CVDys).[3] This type of ischaemic heart disease includes the (combination of) endotypes of vasospastic disease (epicardial vasospasm and/or microvascular spasm) and/or coronary microvascular dysfunction (CMD) defined as an increased microvascular resistance and/or decreased vasodilatory capacity as measured by coronary flow reserve (CFR).[4,5] In addition, non-obstructive CAD can be more or less visibly present at coronary angiography. Microvascular spasm and CMD are often grouped together as underlying causes of microvascular angina.[5] Coronary vascular dysfunction is more prevalent in women than in men, with a study of 1379 INOCA patients demonstrating CVDys in 70% of women with INOCA vs. 43% of men.[6]

Patients with symptoms suggestive of myocardial ischaemia without signs of obstructive CAD have an increased cardiovascular risk compared with persons without anginal symptoms. In more than 10 000 patients with stable angina referred for coronary angiography, the presence of normal coronary arteries or diffuse non-obstructive CAD was associated with an elevated risk of major adverse cardiac events and all-cause mortality

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compared with a reference population without ischaemic heart disease.[7] The worse prognosis is specifically present in patients with combined vasospastic disease as well as microvascular dysfunction.[8,9] In addition to an adverse cardiovascular prognosis, INOCA patients often have persistent symptoms, leading to repeated presentations at the emergency ward, unnecessarily diagnostic examinations targeting obstructive CAD, resulting in a reduced quality of life with impaired working participation.[10–12] Because standard diagnostic tests for anginal symptoms are mainly aimed at evaluating fixed obstructive CAD, CVDys is often overlooked. Accruing evidence shows that CVDys can be properly and safely diagnosed with invasive coronary vasomotor function testing (CFT) and that subsequent tailored treatment leads to reduction of symptoms and improvement in quality of life.[3] This review focuses on contemporary and future care with regards to the invasive CFT, the implementation of this diagnostic method, and patient-tailored treatment in INOCA patients.

Invasive coronary vasomotor function testing

Invasive CFT is currently the only diagnostic option that can comprehensively evaluate all endotypes of CVDys. Current consensus guidelines recommend the CFT to include coronary angiography to rule-out obstructive CAD, pharmacological vasospasm provocation testing, and the assessment of microvascular dysfunction using adenosine.[13] The main advantage of endotyping CVDys is from a prognostic and therapeutic perspective. Prognostically, the combination of worse prognosis is specifically present in patients with combined vasospastic disease as well as microvascular dysfunction. From a therapeutic perspective, standard pharmacological treatment has disappointing results, and current consensus guidelines recommend patient-tailored pharmacological treatment based on the underlying endotype.

Acetylcholine spasm provocation testing

To evaluate coronary vasospasm, incremental doses (usually 2, 20, 100, and 200 μg) of intracoronary acetylcholine are administered in the left coronary artery with continuous monitoring of symptoms and 12-channel electrocardiogram (ECG) to detect electrocardiographic ischaemic changes. Some centres use ergonovine as an alternative to acetylcholine, but this is less effective especially in women.[14] According to the Coronary Vasomotion Disorders International Study Group (COVADIS) expert group criteria, the acetylcholine test is positive for epicardial spasm if recognizable symptoms occur, accompanied by ischaemic ECG changes and an angiographic ≥90% reduction of the coronary lumen. If there are recognizable symptoms and ischaemic ECG changes, but <90% lumen reduction, the diagnosis of microvascular spasm is made. After the highest acetylcholine dose, nitroglycerin is administered to assess coronary vasodilatation and counter possible patient complaints.

Assessment of microvascular dysfunction

After vasospasm provocation testing, microvascular dysfunction is assessed. Using systemic infusion of adenosine, the CFR is determined, defined as the ratio between hyperaemic coronary flow vs. resting flow. This can be done by means of bolus-thermodilution or Doppler.[15] Using an intracoronary guidewire tipped with a Doppler crystal, phasic flow velocity patterns can be measured and the average peak velocity (APV) can be determined. Doppler CFR is defined as the ratio between APV at hyperaemia and APV during resting conditions. The bolus-thermodilution method makes it possible to measure coronary flow by calculating the transit time (Tmn) of a bolus of saline. For this, a saline bolus is hand-injected in triplicate into the coronary artery through the guiding catheter, both at rest and during adenosine-induced hyperaemia, and CFR is defined as the ratio of mean hyperaemic Tmn to mean resting Tmn. Generally, both methods have their advantages and disadvantages. While the quality of Doppler flow velocity measurements is significantly lower than that of thermodilution curves, CFR based on thermodilution tends to overestimate flow reserve at higher values.[15]

An invasively measured CFR < 2 is generally used as a cut-off value for the detection of CMD. Overall, most studies demonstrating the prognostic value of thermodilution-based CFR have used a cut-off value of 2.0, while studies showing a prognostic value of Doppler-based CFR have used a cut-off value of 2.5.[9,16] In addition to CFR, in the same session the microvascular resistance is measured: if thermodilution is used, the index of microvascular resistance (IMR) is determined, if the evaluation is done with Doppler, the hyperaemic microvascular resistance (HMR) is determined.[17] An IMR > 25 U is diagnostic of CMD, while for HMR 2.5 mmHg/cm/s is used as the cut-off value for the diagnosis of CMD.[13]

From a patient perspective, the measurement of CFR and resistance require hyperaemia for which intravenous adenosine is administered. Adenosine is associated with multiple side effects including flushing, chest pain, dyspnoea, and atrioventricular blocks. Furthermore, it should generally be avoided in patients with severe chronic obstructive pulmonary disease and is contraindicated in patients with asthma.

Safety of the invasive coronary vasomotor test

Recent large studies have shown that coronary vasomotor tests can be performed safely. Complication risks of 0–0.7% are found for the occurrence of serious complications such as myocardial infarction, ventricular fibrillation, or death. This is comparable to a CAG with FFR measurement.[18,19]

Our experience

In the Radboudumc, we initiated the CFT programme in 2019. Coronary function tests are performed on an elective basis, ad-hoc CFT after normal angiography is not yet routinely performed. In accordance with the recommendations of the Dutch Society of Cardiology, we perform elective CFT based on the following indications: (i) If

having a definite diagnosis is important to the patient, e.g. to promote acceptance of the disease or to have a clear diagnosis in case of a working dispute. (ii) If having a definite diagnosis is important to the cardiologist, e.g. when medical therapy is not effective and doubts rise about the likelihood of the diagnosis. In 2021, we have performed over 400 CFTs at our cardiology centre. The results of the first 111 procedures were published recently.[21] In these patients that completed CFT (88% female, mean age 54 years), 86% were demonstrated with CVDys. The majority (97%) had coronary spasm, 63% isolated, and 34% combined with CMD. Of the patients with spasm, 52% had epicardial spasm and 48% had microvascular spasm. Isolated microvascular dysfunction (reduced vasodilatory capacity and/or elevated microvascular resistance) was rare, occurring in only 3% of the patients. Our study confirmed the safety of performing CFTs. Overall, there were no fatal or serious non-fatal complications, three patients experienced a (bleeding) complication related to the access site. An example of an INOCA case with demonstrated epicardial spasm and microvascular dysfunction is shown in *Figure 1*.

Novel angiographic techniques to assess coronary microvascular dysfunction

Absolute flow to assess coronary flow reserve and microvascular resistance

With regard to CMD, as mentioned above, both bolus-thermodilution as well as Doppler-based assessment have their disadvantages. The diagnostic process can be improved using metrics that are capable of assessing true coronary flow and microvascular resistance. A novel invasive method has recently become available that is easy, reproducible, and safe: continuous thermodilution assessment of the microcirculation.[20,21] Absolute blood flow and resistance measurements are based on thermodilution and continuous infusion of saline at room temperature through a dedicated monorail catheter (RayFlow, Hexacath), advanced over a pressure/temperature sensor-tipped guidewire. It has been demonstrated that hyperaemic flow measured by continuous thermodilution correlates well with the gold standard PET.[22]

With regards to the patient perspective, no adenosine is required because of the saline-infusion-induced hyperaemia. We have reported on the use of continuous thermodilution-derived measurements in INOCA.[23] In 84 patients undergoing clinically indicated CFT, we found that the absolute resistance (R) value was higher in patients with CMD, defined as abnormal CFR or IMR, than in the control group. Absolute Q was not different between these groups (191 vs. 208 mL/min). Furthermore, we observed that low Q (defined as <198 mL/min) and high R (defined as >416 WU) were associated with the severity of angina. Therefore, continuous thermodilution-derived measurements correlated with microvascular dysfunction and anginal complaints. We did not observe any adverse events related to the use of the continuous thermodilution method.

In the Radboudumc, continuous thermodilution-based assessment of CMD is routinely performed as part of the CFT. The next step would be to validate our findings in a larger cohort, including clinical outcomes. If the diagnostic value is confirmed and prognostic value demonstrated, this method has the potential to replace the bolus-thermodilution method.

Angiography-based physiological assessment of index of microvascular resistance

Novel angiography-derived physiological indices have been developed whose main aim is assessing functional stenosis relevance without intracoronary instrumentation and administration of hyperaemic drugs. These techniques apply computational fluid dynamics or advanced mathematical formulas to three-dimensional reconstruction of vessel lumen to establish the haemodynamic impact of the interrogated stenosis. In addition, for the assessment of CMD, a formula has been developed to estimate an angiographic IMR.[24] A small validation study demonstrated that the angio-IMR correlated well with an invasively measured IMR. If prospectively validated, an abnormal angio-IMR measured at angiography could identify CMD, while a normal angio-IMR with persistent ischaemic symptoms in INOCA would still be an indication for comprehensive CFT.

Treatment

Recommendations for pharmacological treatment of CVDys are mainly based on smaller (non-randomized) studies because large outcome trials are not available.[25] The treatment consists of the main components cardiovascular risk management, anti-anginal treatment, and lifestyle advice.

Cardiovascular risk management

Since classical cardiovascular risk factors also play a role in CVDys, and because intracoronary imaging studies show an overlap in INOCA and atherosclerosis, it is recommended that these are strictly controlled with statins, antihypertensive drugs, anti-diabetic therapy, and lifestyle modifications such as weight reduction and smoking cessation.[13,26] In addition to hypertension treatment for cardiovascular risk management strict blood pressure regulation often provides symptom relief. Statins, in addition to their lipid-lowering effect, are recommended because of their beneficial effect on endothelial function and a potential beneficial effect in the reduction of vasospastic angina.[27,28] This may be challenging in this predominant female population in relation to their higher susceptibility for side effects. When epicardial spasm is suspected, triggers such as smoking/co-smoking and drug use (including cocaine or amphetamines) should be strongly discouraged. Angiotensin converting enzyme(ACE) inhibitors and angiotensin II antagonists are recommended, not only as effective antihypertensives, but also because they improve endothelial function and have a beneficial effect on both CMD and epicardial vasospasm.[27,29] The role of aspirin in the treatment of CVDys is still unclear, but might be considered when non-obstructive CAD is clearly present.

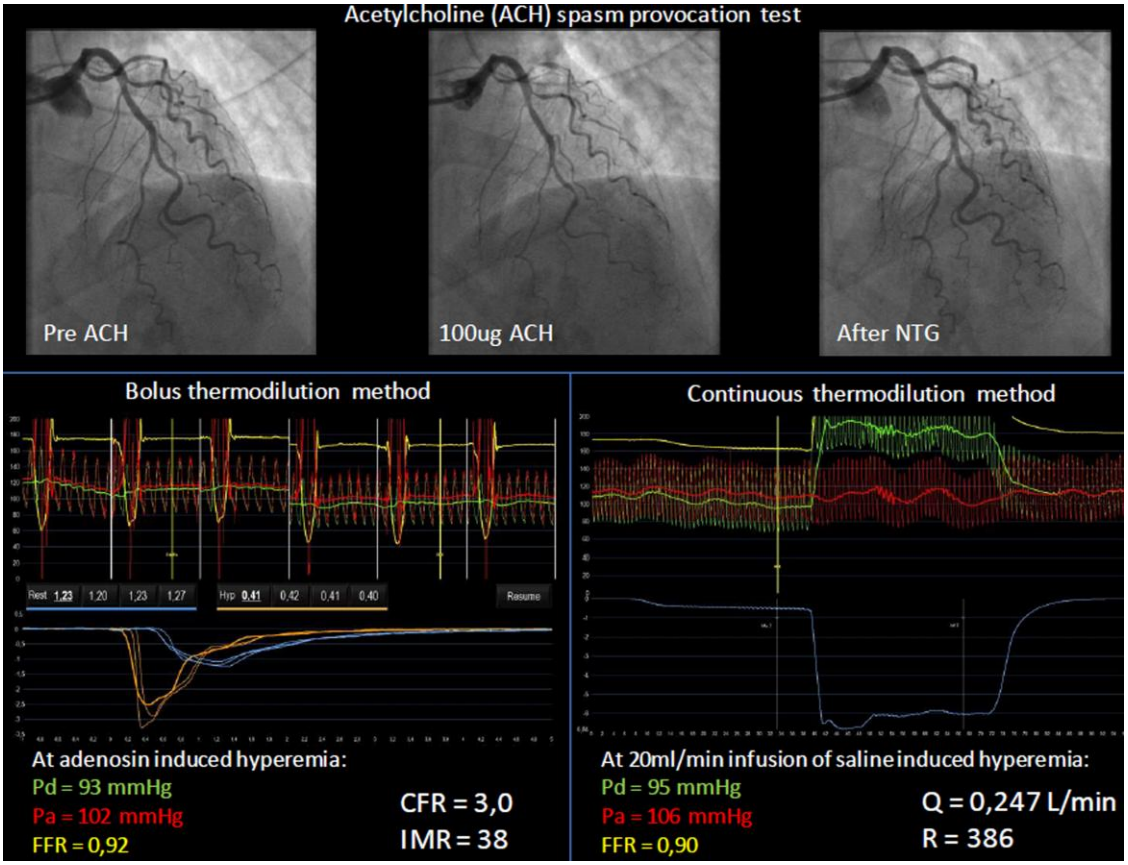

Figure 1 Example of a INOCA case (50-year-old female) with combined epicardial spasm and microvascular dysfunction.

Anti-anginal treatment

In addition to ACE inhibition, the additional anti-anginal treatment should be based on the results of the CFT, taking the (combination of) different coronary vascular endotypes into account.[13] Patient-tailored medical treatment guided by invasive CFT has been shown to improve anginal symptoms up to 1-year follow-up in the landmark CorMicA trial.[3]

In vasospastic CVDys, the first-line therapy consists of a (non-) dihydropyridine calcium-channel blocker and/or a short-acting nitrate to reduce the occurrence of vasospastic attacks.[13] The dosages of these calcium blockers vary among patients and may exceed commonly recommended dosages. It is recommended to avoid non-selective β-blockers, such as propranolol, because it has been described to exacerbate coronary spasm.[30] If the effect on the complaints of first-line treatment is insufficient, we consider the following second-line pharmacological options: the addition of a long-acting nitrate, the combination of a non-dihydropyridine with a dihydropyridine calcium antagonist, or nicorandil. Nicorandil has been shown to be an effective agent for epicardial spasms and can be added if symptoms are insufficiently controlled.[31]

In CMD with predominantly resting symptoms, calcium-channel blockers are recommended because they have been shown to be effective in both epicardial spasms and CMD.[25] Both non-dihydropyridines and dihydropyridines calcium antagonists can be considered. β-Blockers are recommended in patients with predominantly exercise-related symptoms, also depending on resting heart rates.[13] In patients with refractory symptoms and/or intolerance to the first-line medication, other second-line anti-anginal medications such as nicorandil or ranolazine may be given.[13] Ranolazine is a sodium channel blocker that reduces intracellular calcium in cardiomyocytes leading to improved intraventricular relaxation, potentially improving microcirculation. A randomized trial in 81 patients showed that ranolazine improves symptoms and myocardial perfusion in patients with a CFR < 2.5.[32]

Third-line medication includes Trimetazidine, an anti-ischaemic metabolic agent that improves myocardial glucose utilization through inhibition of fatty acid metabolism. It improves angina and stress testing results when compared with conventional therapy. The use of central agents like imipramine may be considered to mitigate anginal symptoms.

Lifestyle adjustments

Many patients with CVDys experience limitations their daily life and activities because of chronic, severe symptoms. This is especially hampering because it often concerns middle-aged women who are working and/or have a family with children. While there is little scientific literature available on the influence of lifestyle changes on symptoms, in our centre we have over 5 years of experience with the guidance of these patients by a specialized

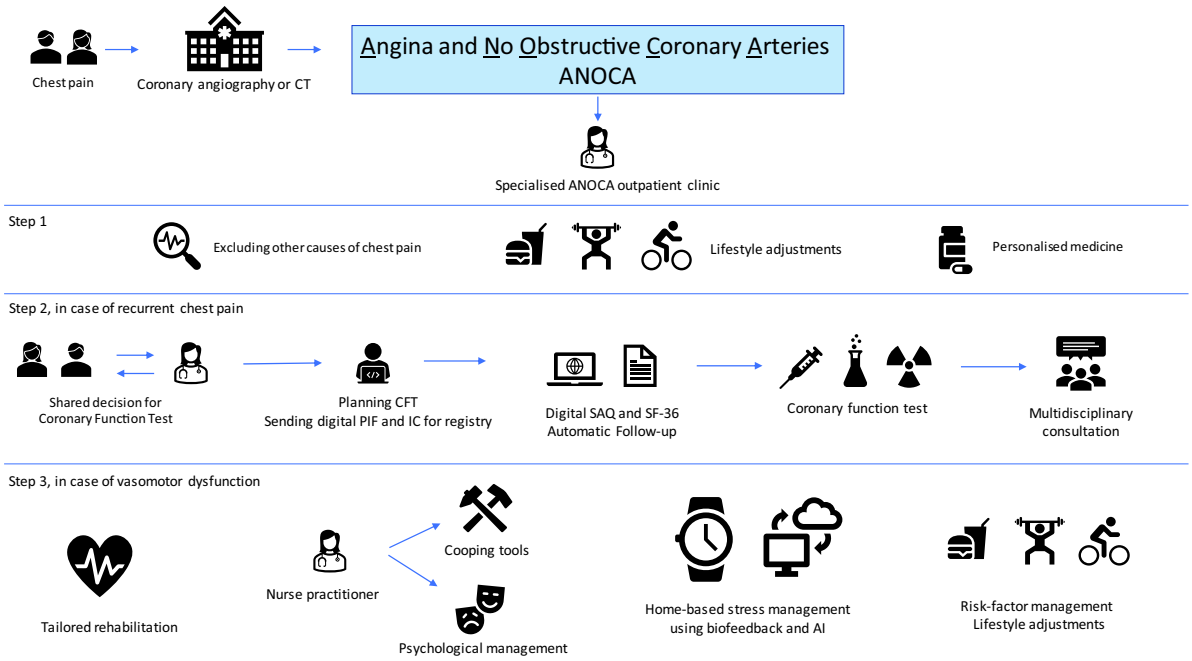

Figure 2 Flow chart radboudumc ischaemia with no obstructive coronary arteries specialized clinic.

nurse practitioner. The nurse practitioner focuses on exercise, fatigue, and stress reduction. In addition, the expertise of a psychologist and/or occupational therapist may be needed. Acceptance of the disease is a major problem in these patients, due to persistent and often fluctuating symptoms over time.

Exercise has been shown to reduce symptoms and improve exercise tolerance.[32] To date, no exercise programme exists that is tailored to patients with INOCA. In our experience, a regular cardiac rehabilitation programme is often too strenuous for INOCA patients with seriously debilitating symptoms. Based on in-depth interviews multiple of our patients, several important barriers to perform physical activity were identified: anxiety to develop symptoms, mental pressure leading to symptoms and uncertainty of their physical limitations due to variation of symptoms over time. We refer patients wishing to participate in an exercise programme to rehabilitation under supervision of a healthcare professional with knowledge of INOCA, who knows how to train and give advice on coping with symptoms during or after physical activity, leading to a feeling of security and being taken care of. Mental stress and/or overstimulation can trigger symptoms, probably related to vasospasm.[33] Patients with severe symptoms often report concentration problems and symptoms triggered by work deadlines or outside stimuli like traffic noise and social events. It could therefore be important to provide patients with instructions on how to cope with stress and to avoid stressful stimuli. Possible interventions offered include mindfulness, yoga, Tai Chi, or walking in nature. Furthermore, we are now investigating whether the use of a remote stress-reducing programme on the smartphone (WavyTunes), using biofeedback and artificial intelligence, is a helpful additional tool for on-demand use.

Future therapies and coronary function test

The CFT programme provides a unique opportunity to improve our understanding of therapeutic options for vascular dysfunction and to investigate novel therapies.

In the current review, and current consensus guidelines, treatment is roughly aimed at the INOCA endotypes vasospastic disease and/or microvascular dysfunction. However, CVDys can coexist with or without obstructive and non-obstructive atherosclerosis.[34] The first setting is illustrated by the persistence or recurrence of angina after a percutaneous coronary intervention (PCI) which affects about 20–40% of patients during short-term follow-up.[35] This appears to be true even when PCI is 'optimized' using physiology-guided approaches. Coronary vascular dysfunction might play an important role in these patients. Furthermore, with regards to CVDys, the CFT endotypes are functionally divided into (combinations of) impaired dilatation to flow, increased minimal resistance to flow, and inappropriate constriction. However, these functional abnormalities can be regionally or diffuse, transient, or permanent. Finally, while CVDys is identified with CFT, the underlying disease may include many other cardiovascular conditions, including myocardial infarction, nonischaemic cardiomyopathies, takotsubo syndrome, and heart failure (HF) (especially HF with preserved ejection fraction).[36] Many molecular, functional, and structural mechanisms may be involved and are related to the underlying disease. Future research should focus on these complex pathophysiological interplays and targeted treatment.

With regards to novel therapies, we are currently performing a randomized-controlled trial in which the effect of calcium-channel antagonists on vasomotor dysfunction endotypes at repeated invasive CFT are compared with placebo [EDIT-CMD (Efficacy of Diltiazem to

Improve Coronary Microvascular Dysfunction: A Randomized Clinical Trial); NCT04777045].

Establishment of an expertise centre and NL-coronary function test

In the Netherlands, we are one of the first centres with a specialized INOCA outpatient clinic, including the capabilities to routinely perform CFTs. Using electronic outpatient clinic and post-CFT electronic questionnaires, data on anginal symptoms, quality of life, and clinical outcomes are automatically collected. These are stored in an electronic data capture system, including al peri-procedural CFT data. A summary of our logistics is illustrated in *Figure 2*. With regards to CFT, since the recent European Society of Cardiology on Chronic Coronary Syndromes emphasized the role of invasive diagnostics, multiple centres are interested to perform these procedures.[37] As an expert centre, we stimulate knowledge transfer, including the opportunity to learn the performance of CFTs in our cathlab, share the protocols and standard operating procedures, and supervision of CFTs on remote locations by dedicated operators. Furthermore, web-meetings are organized with colleagues where complex patients and CFTs can be discussed.

All visiting centres are invited to participate in the Dutch registration of invasive CFTs: NL-CFT (Dutch-CFT). The main objectives of this initiative are to improve the understanding of the underlying pathophysiology in CVDys, the diagnostic CFT procedure, and patient-tailored treatment. This includes the performance of registry-based randomized clinical trials using NL-CFT as the underlying structure. Finally, it provides a means of quality control for centres performing CFTs. By 2022, ~20 centres are expected to participate in NL-CFT.

Conclusion

In the current review, we emphasize the importance of invasive diagnostics and tailored therapy in patients with INOCA. The importance of the diagnostic CFT procedure is described, including future components including angiography-derived physiology and invasive continuous thermodilution. Furthermore, the main components of treatment are discussed. Future directions include the national registration ensuring a high quality of INOCA care, besides a potential source to improve our understanding of pathophysiology in CVDys, the diagnostic CFT procedure, and tailored treatment.

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