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NEWSLETTER

ISSUE 6 October - December 2021

INOCA INTERNATIONAL at COVADIS

COVADIS
Coronary Vasomotor Disorders International Study Group

INOCA International were honoured to be invited to present at the 9th COVADIS Summit. What a great pleasure it was to spend time with so many leading minds in INOCA and to be privy to the current thoughts, ideas and discussions taking place there.

COVADIS are committed to excellence in everything they do and this was clearly evident in their determination to invite and to carefully listen to the INOCA patient voice.

COVADIS are as determined as ever to do all they can to raise awareness, further education and improve care for INOCA patients. INOCA International are delighted to make the commitment to support and disseminate the ongoing and outstanding work of COVADIS!

This year's Summit brought together leading cardiologists from around the world, with discussion centred around a clinical case of a 58-year old man, referred for CT coronary angiography for evaluation of chest pain. The patient had previously received a coronary artery stent for a blockage in his left coronary artery, but anginal chest pain persisted. Testing confirmed microvascular angina due to small vessel problems and spasm. The case prompted great discussion and clearly showed the need for testing beyond the angiogram for ongoing angina symptoms.

> Maria George - "*Many patients are still reporting that a clear angiogram marks the end of cardiac testing and a return to primary care, but it is widely accepted now that this is where more detailed testing should in fact begin. We need to encourage thinking beyond the angiogram when indicated, instead of leaving patients to cast around in a system loop of repeat attendances and testing.*"

Prof Noel Bairey Merz "*We were pleased to have input from INOCA International patient representative Maria George, whose remarks added to our meeting.*"

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For our Facebook Information Page
https://www.facebook.com/groups/491395198372627

We also have a Twitter page
https://twitter.com/InocaInternati1

Private INOCA Case Discussion Group and Resource Centre for Doctors
MedShr.it/INOCA

IN THIS ISSUE

LAUNCHING

INOCA INNOVATIONS

An INOCA International special publication which, when considered appropriate, will be issued alongside the INOCA International Newsletter to highlight recent research, papers, journal articles and publications about INOCA, with dedicated narratives from the authors themselves.

Check out the **INOCA INNOVATIONS** first Issue included with this Newsletter!

VIDEO INTERVIEWS

INOCA International are delighted to add two new video interviews to our INOCA MATTERS series – the series where we talk to specially invited guests about INOCA.

Professor Mario Marzilli and **Professor John Beltrame** are both very supportive members of our INOCA International Medical Advisory Board. Both of these amazing professors are directly involved in research and education and are also on the front line treating patients. The wealth of knowledge our Advisory Board Members have is truly invaluable and we are so very grateful to have their ongoing support and their expert knowledge in INOCA!

Professor John Beltrame

Professor Mario Marzilli

As always, all our INOCA videos can be viewed free of charge on our website. To view these amazing interviews – and many more – please visit the INOCA Matters page at – https://www.inocainternational.com/inoca-matters/

CMIS TASK FORCE

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The CMIS Task Force is a newly launched initiative involving 12 world renowned experts who have come together to further understanding in CMIS (Coronary Myocardial Ischaemic Sydrome).

For many years the main focus of diagnosis and treatment in ischaemic heart disease has centred around the atherosclerotic universe. The CMIS Task Force seek to encourage a wider perspective and a more inclusive view of the possible causes and treatment of Ischaemic Heart Disease by raising awareness and by encouraging a patient tailored approach.

CMIS hosted an excellent webinar this month with plans to launch more in the New Year. With so many global experts in one place this really is an incredible resource!

https://cmistaskforce.eventsform.com/hcp-confirmation/

MEDSHR

INOCA International have been working in collaboration with the amazing team at MedShr to create a brand new INOCA group.

THE INOCA INTERNATIONAL CASE DISCUSSION GROUP AND RESOURCE CENTRE ON MEDSHR!

(This is a private group for Doctors)

This Group offers a unique opportunity for Doctors around the world to connect with each other to share ideas and to openly discuss INOCA cases in a GDPR, GMC and HIPPA compliant environment. INOCA International have a truly superb Medical Advisory Board and many of our Board members will be contributing to discussions in Group when their schedules allow. MedShr currently has over 1.7 million members in 190 countries, so this is a fantastic opportunity to reach an even wider audience!

Dr Asif Qasim Founder and CEO of MedShr - *"It's been great to see the response on MedShr to the launch of the INOCA International group. Managing patients with myocardial ischaemia with unobstructed coronary arteries is complex and requires further research. We're looking forward to seeing both the lectures and case discussions around this and would like to invite doctors to join the discussion and post their own clinical cases on MedShr"*

medshr.it/inoca

MedShr
The App for Doctors

N.B. Nothing in this newsletter should be considered in any way as advice or recommendation. All information contained in this newsletter is an opinion only and is shared here only in the hope that is it of interest to other patients and medical professionals. Always consult your own medical practitioner before trying any new medications or therapies and before changing any of your current routines.

INOCA TRILOGY PART 2
DIAGNOSTIC TESTING IN INOCA

This article has been written by an INOCA patient and has been checked by a member of our Medical Advisory Board

The first step towards optimal treatment of INOCA conditions is getting a diagnosis. A definitive diagnosis of the underlying mechanism of the disease is very important in order to put together a successful treatment plan. This can be challenging as the coronary microvasculature cannot be directly visualised by the standard coronary angiogram, but there are several techniques available however to assess coronary microvascular function. Testing for INOCA conditions is an evolving area of Cardiac Medicine which is improving all the time. Here we outline just some of the tests and processes currently used to diagnose INOCA.

LISTEN TO THE PATIENT

This is the most important first step on the journey to diagnosis. It is vital to listen to and believe the patient. Far too often when the standard cardiac tests show clear coronary arteries, an INOCA patient is sent home having been told there is nothing wrong with their heart, or is referred for example for extensive GI testing, or made to believe that it is all in their heads. If you listen carefully to the patient's symptoms there are often clues that the patient is suffering from an INOCA condition rather than (or as well as) traditional Coronary Artery Disease (CAD). For example, chest pain can often last for much longer than 30 minutes, symptoms can come on at rest without any obvious trigger and can often occur at night (in the case of Coronary Artery Spasm).

There is often extreme fatigue and quality of life of INOCA patients can also be reported as much worse than those with CAD. These are just a few of the clues which might be revealed by listening carefully to a detailed patient history. Also, when a patient with CAD continues to have anginal symptoms after a procedure to clear blockages in their coronary arteries, this too could be a sign of an INOCA condition.

STANDARD CARDIAC TESTS

Standard tests such as Blood Tests, ECG's, Echocardiograms and Angiograms can sometimes appear to suggest clear coronary arteries, but sometimes there can also be subtle clues here too. For example, sometimes Troponin can be slightly raised and Stress ECG's can show small changes like inverted T-waves. These are often dismissed as not relevant when they too could be signs the patient is suffering from an INOCA condition. A treadmill exercise test can be informative to highlight how well a patient can exercise, what are the reasons for stopping, whether anginal symptoms occur, and whether there are signs of heart strain on the ECG. This being said, some patients with coronary spasm can do well on an exercise test, and the clinician should keep this in mind. Hence, other tests may be needed.

SCANS

STRESS CARDIAC MRI

Cardiac MRI (CMR) imaging is now one of the most widely used non-invasive tests to diagnose patients with INOCA Conditions, though it is still not available everywhere.

An MRI machine is basically a large magnet which can create images of what is going on inside the patient's body. Before any testing is done, a cannula (a needle attachment) is put into each arm. The patient will be asked to lie on the movable bed, given headphones and a button to press if you need the testing to stop at anytime. The bed then moves inside the machine. The machine is rather noisy, but focusing on the instructions that are being asked may help block out the sound. At first, the scan is done at rest and pictures taken. Then a chemical stressor is given to the patient, (this means that an injection of a liquid is given through the needle in your arm),increasing their heart rate to mimic exercise but without you actually having to do exercise. The patient may experience angina symptoms but this part of the test only lasts a very short time. The other cannula, (the needle in the other arm) is used to give the contrast agent which is visualized by the scanner when the contrast passes through the heart.

INOCA TRILOGY PART 2
DIAGNOSTIC TESTING IN INOCA

This article has been written by an INOCA patient and has been checked by a member of our Medical Advisory Board

This aspect provides information on heart blood flow at rest and during the stress test. The MRI scanner is useful for revealing abnormal variations in blood flow in patients with CAD and/or small vessel problems in the heart. The images generated both at rest and during stress are compared and blood flow is calculated CFR (Coronary Flow Reserve). If blood flow is reduced during the stress segment of the scan compared with the rest part of the scan, then these figures are used to evaluate Coronary Microvascular Dysfunction.

CHALLENGE ECHOCARDIOGRAPH

Another non-invasive option is Echocardiography or Stress Echo. This involves having electrodes placed on the skin and being wired to a machine that measures electrical impulses in the heart. (This is a practice that anyone who has a cardiac issue is familiar with as this is what happens when you have a standard ECG). Then the patient may have a cannula or cannulae inserted into their arms. Throughout the test, clinicians will take images of the heart at rest, during stress, and after stress.

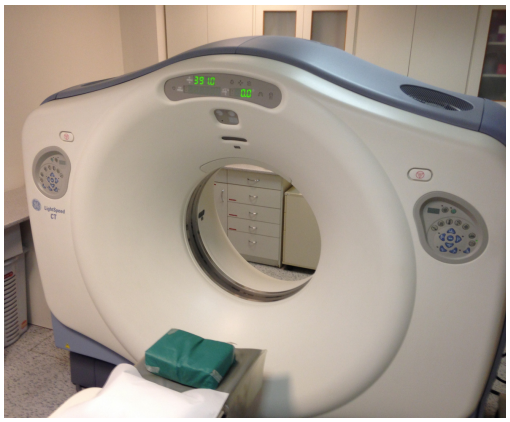
Depending on whether the stress element is induced chemically or by actual exertion, the patient may be asked to walk briskly on a treadmill to increase their heart rate, or maybe cycle on a stationery exercise bike. A gel will then be put onto the chest and a wand shaped camera is run by hand, over the skin with a little pressure being applied, to create live images of how the heart is performing. Again, coronary blood flow is assessed at rest and during stress and the resulting images are then compared.

POSITRON EMMISSION TOMOGRAPHY (PET)

During a PET scan the patient will receive a low dose of a radioactive substance administered into their arm via a cannula. The PET scan images blood flow in a similar way to MRI, except the PET scan is detecting changes in the tracer signal. The scanner works by detecting the small safe amount of radiation given off by the substance injected into the patient's arm.

The scanner itself looks like a large donut. The patient will be asked to lie on a bed that will be moved into the scanner ring. A chemical to stress the heart is then administered. The patient may experience angina symptoms during this phase, but a rescue medicine is always on hand to relieve any symptoms so they will not be experienced for long. The blood flow throughout the heart will be monitored at rest as well as during stress to identify any areas of reduced blood flow. The scan usually takes around 30 to 60 minutes.

INOCA International



FUNCTIONAL CORONARY ANGIOGRAPHY

Invasive coronary angiography is a procedure where a standard angiogram is initially carried out, then a very fine guidewire is used with a vasodilator such as adenosine being administered to stress the heart. The coronary blood flow is monitored throughout the process to check for microvascular dysfunction. To test for microvascular spasm a naturally occurring substance called acetylcholine is administered during the angiogram.

The patient won't know when it is introduced but is asked to describe any symptoms they experience. Monitoring of symptoms and changes in the ECG and blood flow in the heart artery can indicate and diagnose microvascular spasm. Again, as in some of the previous tests described, rescue medicine is on hand to relieve any angina symptoms the patient may experience. So please be reassured that any angina should be transient and not be experienced for long. There is a small risk of a slow or fast heart beat after receiving the acetylcholine test. Again, if this occurs, it is not expected to last for long.

Our thanks go to the patient authors of this trilogy article and to the Medical Advisory Board member who very kindly fact checked the article prior to publication.

Part 3 of the Trilogy series will appear in the next Newsletter and will be address

'TREATMENTS IN INOCA'

THE VAGUS NERVE

by Dr Ailsa Care

It seems these days that everyone is talking about the vagus nerve and how improving its function can improve our health in many different ways. So what is the vagus nerve? It is a long nerve which connects our brain to our gut and other organs. It is a 2 way connection so carries information from the brain to our internal organs (heart, lungs and gut) and vice versa.

The vagus nerve helps to control essential automatic functions such as pulse rate, breathing, blood pressure as well as digestive functions like stomach acid, digestive enzyme production and also stimulates gut motility (that is a muscular contraction that moves matter down the gut to make room for more food coming in. I call it the "move on down the bus" function!)

The vagus nerve responds to stress by triggering the sympathetic or "fight/flight" response which increases our pulse, blood pressure and breathing rate to get blood/oxygen to our muscles to enable us to run away from danger faster and therefore survive. Once the danger has passed what is supposed to happen is that we return to the default state or parasympathetic "rest/relax/digest".

The problem with modern life is that it is no longer a short term acute stress like a tiger chasing us but frequent/chronic stress that keeps us in "fight/flight" most of the time.

Common symptoms related to this chronic sympathetic nervous system activation include: tense/hard muscles, sore neck and shoulders, headaches, back pain, grinding teeth at night, cold hands and feet, excessive sweating, feeling nervous, irritability, lack of energy, feeling tearful, chest pains, shortness of breath, irregular heartbeat, high blood pressure, poor digestion, constipation (not moving on down the bus!) The list goes on...

So what can we do to help?

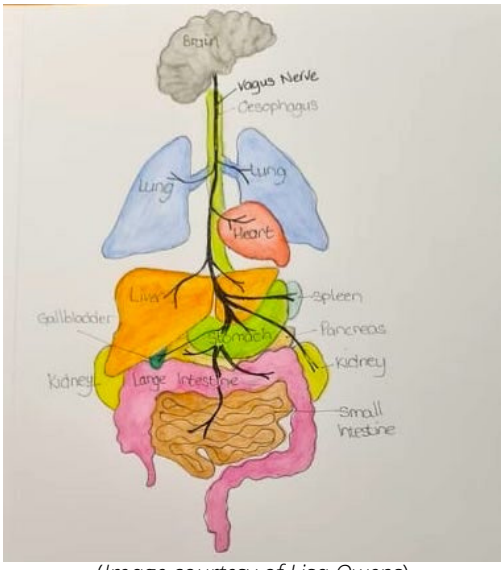
Here are some tips for you to try. It is not about doing all of them. Think of it like a pick and mix, try different techniques and find the ones that you personally find helpful.

Movement

Mindful movement like yoga, Tai Chi, Qi Gong, walking

Breathing exercises - meditation and mindfulness

Breathing should be deep and slow filling your lungs with the exhalation longer than the inhalation. Aim to slow it down to around 6 breaths per minute



(*Image courtesy of Lisa Owens*)

Good balanced Nutrition

There is a strong connection between the vagus and digestion

Eat a balanced diet including probiotic (contain healthy bacteria e.g kefir, sauerkraut, kimchi, kombucha, live yoghurt) and prebiotic (fibres that feed the healthy bacteria like onions, garlic, leeks, chicory) foods

Cut down in simple sugars and high density carbohydrates

Eating fibre stimulates vagus impulses to the brain.

Ensure you chew your food thoroughly

Laughter

- Having a good laugh boosts your mood, strengthens your immune system and stimulates the vagus

Singing/chanting/humming

- Activates the vagal brake on the heart's pacemaker which triggers a parasympathetic response (rest and relax)

Massage

- Body/foot/head massage stimulates the vagus and stimulates the release of oxytocin from the brain which in turn inhibits the release of stress chemicals

Other

- Playing a wind instrument
- Dancing
- Cold water face immersion (safely!)
- Loud gargling with water
- Positive affirmations
- Positive social connection
- Intermittent fasting
- Prayer
- Fish oils (EPA/DHA) - please consult your Dr or pharmacist before taking as they can interact with some medications
- Sleep
- Laying on your right side
- Acupuncture
- Sun exposure - ensuring of course that you don't burn

The Basic Exercise (from the book Accessing the Healing Power of the Vagus Nerve by Stanley Rosenberg)

- Test first - rotate your neck to the right as far as it can comfortably go. Notice any strain or pain that may occur. Rotate your neck back to the centre. Now, rotate your head to the left as far as it can comfortably go and also notice any pain or strain that you may feel. Notice how far both sides are able to rotate.

THE VAGUS NERVE
(continued)
by Dr Ailsa Care

Basic Exercise – lie comfortably on your back or sit up with your spine straight and in line with your head. Weave the fingers of both hands together and place them tightly behind the back of your head

- Keep your head still and moving your eyes only, look to the right as if you are gazing at the tip of your right elbow. Stay in this position for about 30-60seconds until there is a sign of release from the autonomic nervous system in the form of a sigh, yawn or swallow
- Move your eyes back to looking straight ahead and repeat on the left side.
- After completing the exercise test the rotation in your neck again to see if there is any
- improvement in the range of neck rotation, sensation of strain, stiffness or pain.

Vagus Nerve Stimulator e.g Sensate device – **Please note do not use if you have a pacemaker.** This is a large pebble like device which is worn around the neck on a lanyard and sits over your breast bone (sternum). Once switched on it connects via bluetooth to an app on your phone which plays specially designed music and coordinates with the vibrations from the Sensate device. A number of different tracks can be selected depending on time and preference.

Personally I have found it gave me a very deep feeling of relaxation and it has been a great help in managing the stress of my busy GP days.

This week saw the launch of the first Case Presentation in the INOCA Case Discussion Group where doctors can connect with one another to share ideas in INOCA. Professor Marzilli presents a very comprehensive case for discussion. Doctors – Please make sure you have activated your joining link and verified your email address so you can be admitted into the group. If you don't have a link, please click on MedShr.it/INOCA and follow the instructions on the screen. *(This group is for Doctors only)*

We were very sad to learn this month of the death of
Professor Atillio Maseri

It seems no matter where you go or who you speak to, Professor Maseri is remembered with an affection portraying a valued colleague, a wise teacher and a true friend.

I didn't ever meet Professor Maseri, but I feel sure I would have liked him.

Thank you for everything you did to raise awareness of INOCA Professor Maseri and thank you also for teaching with such kindness, those who teach us now.

We are all in a better place – because of you.

In tribute to a great man, in medicine and in life

R.I.P.
Professor Atillio Maseri
1937 to 2021

Introducing ...

INOCA INNOVATIONS

(Image courtesy of Issy Walker)

The special publication issued alongside the

INOCA International Newsletter

Highlighting recent research, papers, journal articles and publications chosen by INOCA International, with dedicated narratives from the authors themselves.

The Theatrics of Small Coronary Arteries

Professor Kim Dora and Professor Raimondo Ascione

Human coronary microvascular contractile dysfunction associates with viable synthetic smooth muscle cells

by Professor Kim A Dora, Professor Raimondo Ascione et al.

Cardiovasc Res. 2021 Jun 26; cvab218; MID: 34173824 ; DOI: 10.1093/cvr/cvab218
Press release: https://www.bristol.ac.uk/news/2021/august/cardiac-microvascular-dysfunction-.html

New evidence suggests that when heart micro-arteries are damaged, the resulting microvascular dysfunction is associated with many forms of heart disease and cardiac syndromes. This condition is also referred to as Ischaemia with Non Obstructed Coronary Arteries (INOCA). One of these conditions is microvascular angina, affecting thousands of patients globally. One obvious issue is that microvascular dysfunction cannot be assessed by cardiac scans currently.

Normally, the delivery of oxygen and nutrients to each cardiac muscle cell is effectively and efficiently achieved by small changes in the diameter of these small intramuscular arteries. These micro-arteries intrinsically respond to changes in pressure – when pressure goes up, they contract – called the myogenic response. This forms a level of vascular tone from which other agents can rapidly increase and decrease artery diameter, in a beat-to-beat basis.

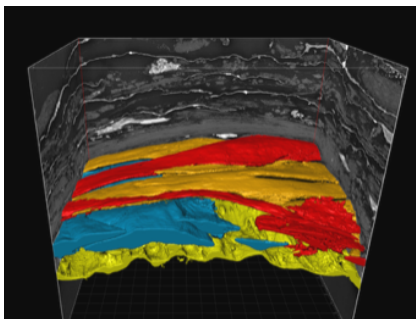
In a typical modern "healthcare theatre" contrast dye are injected into the blood stream to visualise the larger coronary circulation for diagnosing and treatment of atherosclerotic plaques and blockages. However, these modern scans are not powerful enough to visualise the tiny, hair-size micro-arteries. Therefore, current diagnostic systems cannot help patients with INOCA to work out the reasons for their symptoms.

Hence a key question remains: how can we study the heart micro circulation to help these patients?

To complicate matters, the acute and chronic changes linked to poor blood supply to the heart, also called ischaemia, and influenced by vasodilator drugs, thrombosis, inflammation, tissue damage, fibrosis and wall remodelling are impossible to separate when making assessments in these patients.

To shed some light in this area, research is now opening the curtains to advanced "laboratory theatres", where special and more in-depth investigations can be undertaken, in so doing revealing the complexities of these small coronary arteries that hold the resistance to blood flow within the walls of the human heart (and everywhere else in the human body).

Abnormalities in structure and function occur in the micro-arteries of human hearts in regions well beyond the large arteries which develop the atherosclerotic blockages that trigger the need for stents or bypass surgery



The stage is set. Three-dimensional scanning electron micrograph of the wall of a human coronary micro-artery after showing it developed myogenic tone in the laboratory. The blood flows to and from the audience, below the endothelial cell surface (see Cardiovascular Research article).

Now the new research stage is set (see image) to resolve the reactivity of micro-arteries. The main players or actors in this story are the endothelial cells (yellow) normally in contact with the blood, the circumferencial smooth muscle cells (red/orange) responsible for changes in diameter, and a distinct and very interesting/puzzling set of smooth muscle cells (blue) that are aligned in the longitudinal axis, parallel to endothelial cells. These cellular players sit within the backdrop of collagen, elastin and a host of other cells.

By isolating and studying both structure and vasoreactivity in these tiny arteries and the roles of these key actors we can begin to untangle alterations that link to abnormalities in myogenic tone. This is achieved by taking small heart samples, that are otherwise discarded, from patients with no large coronary artery blockages and undergoing valvular cardiac surgery, and also from organ donors. Remarkably we find 44 percent of the micro-arteries from patients have abnormal myogenic tone despite retaining cell viability. This contractile abnormality is associated with an excessive presence of a molecule called caldesmon within the smooth muscle cells and with poor cellular alignment compared to micro-arteries with normal myogenic tone from the other 66 percent of patients, and all the organ donors.

It is now well established that thousands of patients, mostly postmenopausal women, have angina-like symptoms despite their coronary angiogram showing no obvious blockages of the large epicardial arteries in the heart that are usually treated with stent or bypass. Other patients seem to develop heart failure associated with either the contraction or the relaxation of their heart for no obvious reasons.

The next big goal will be to develop approaches and collaborations to combine the two theatres, cardiac surgeons, cardiologists and laboratory scientists in efforts to more clearly understand INOCA with the aim of improving the performance of each patient's heart.

ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–11
doi:10.1093/eurheartj/ehab653

STATE OF THE ART REVIEW
Heart failure and cardiomyopathies

Untangling the pathophysiologic link between coronary microvascular dysfunction and heart failure with preserved ejection fraction

Aish Sinha , Haseeb Rahman , Andrew Webb , Ajay M. Shah , and Divaka Perera *

Dr Aish Sinha speaks to INOCA International about their latest publication

Nearly half of all patients with angina have non-obstructive coronary arteries (ANOCA). ANOCA itself is an umbrella term comprising distinct entities; these include coronary microvascular disease (CMD) and coronary vasospasm. Patients with CMD have an impaired quality of life and are at a higher risk of adverse cardiovascular outcomes; this includes heart failure. Heart failure is classified into two broad groups: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

Several important pathophysiological differences exist between these two disease entities, but, in summary, HFrEF is characterised by an abnormality of the pumping mechanism of the heart muscle, whereas HFpEF is characterised by an abnormality in the ability of the heart muscle to relax and fill up with blood. Our understanding of the disease processes underlying HFrEF has been bolstered by years of research in this field, resulting in the development of several disease-modifying therapies available for patients with HFrEF. However, our understanding of the disease processes underlying HFpEF remains incomplete, which has resulted in a paucity of effective disease-modifying therapies.

Dr Aish Sinha

Dr Haseeb Rahman

Dr Andrew Webb

Professor Ajay Shah

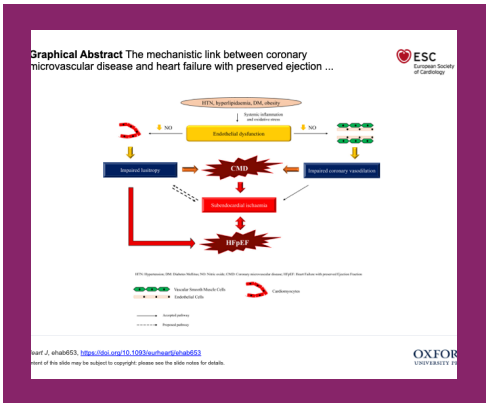
Professor Divaka Perera

Furthermore, it is becoming evident that HFpEF is a heterogeneous disease condition comprising several distinct endotypes.

Numerous recent studies have demonstrated a high prevalence of coronary microvascular dysfunction in patients with HFpEF, which is suggestive of a specific endotype of HFpEF: the CMD-HFpEF endotype. In this review article, we discuss the pathophysiological mechanisms linking coronary microvascular dysfunction with HFpEF.

We hope that a better understanding of the underlying mechanisms will result in the development of novel therapies targeting the specific disease processes associated with the development of CMD-HFpEF.

Please click on the link to read the full article – – https://academic.oup.com/eurheartj/advancearticle/doi/10.1093/eurheartj/ehab653/6371296



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Journal of the American College of Cardiology

JACC Journals › JACC › Archives › Vol. 78 No. 13

Coronary Microvascular Dysfunction Across the Spectrum of Cardiovascular Diseases: *JACC* State-of-the-Art Review

JACC State-Of-The-Art Review

Marco Giuseppe Del Buono, Rocco A. Montone, Massimiliano Camilli, Salvatore Carbone, Jagat Narula, Carl J. Lavie, Giampaolo Niccoli, and Filippo Crea

J Am Coll Cardiol. 2021 Sep, 78 (13) 1352–1371

Dr Rocco Montone speaks to INOCA International about their latest publication

This review comes from an international collaboration between experts involved in the research and in the clinical management of patients with CMD, under the guidance of Prof. Filippo Crea, senior author of this work.

The purpose of this review, just published in JACC, is to describe the pathophysiological mechanisms of CMD and its mechanistic and prognostic role across different cardiovascular diseases, including ischemia with non-obstructive coronary arteries, CMD in patients with co-existing obstructive coronary artery disease, non-ischaemic cardiomyopathy, takotsubo syndrome and heart failure, especially the phenotype associated with preserved ejection fraction (the so-called "HFpEF").

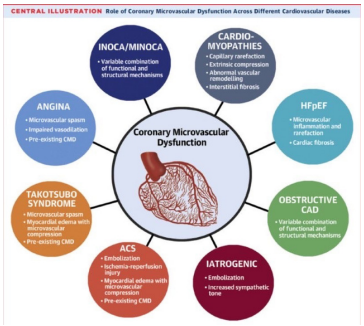
After a detailed description of functional and structural alterations along with the underlying molecular mechanisms involved in the pathogenesis of CMD, an important section dealing with the diagnostic approach to CMD is present.

Indeed, multiple invasive and noninvasive techniques assessing the function and integrity of coronary microvasculature are now available and are required to evaluate the presence of CMD.

In this review, all currently available diagnostic techniques, with their pros and cons, are extensively described and interesting clinical cases of CMD in different clinical scenarios are reported.

Finally, this review focuses on therapies targeting CMD with suggestions for future studies addressing the knowledge gaps in the management of these patients.

In particular, due to the emerging role of CMD as common denominator in different clinical phenotypes, additional research in this area is warranted to provide personalized treatments in this "garden variety" of patients.



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Indeed, to date, there are no specific therapeutic strategies targeting CMD validated by large-scale randomized clinical trials, and therefore, treatment of patients with CMD should be targeted on the risk factors and specific phenotypic presentation. In this review, currently available therapeutic options are reported along with several upcoming promising therapeutic approaches to be tested in future studies.

To view the full article please click on the following link -

https://www.sciencedirect.com/science/article/abs/pii/S0735109721057799X?dgcid=author