

CARDIALYSIS

Clinical Trial Management - Core Laboratories



Core Laboratory services

The allround trial specialist in cardiology Leading since 1983

cardialysis.com



Core Laboratory services

Cardialysis has over 30 years of experience acting as an independent core laboratory in clinical trials in cardiology. To date we have been involved in over 250 clinical trials varying from phase II and phase III clinical studies, registries, post-marketing studies and Investigator Sponsored Studies. Continuous innovations and application of imaging modalities in different settings such as animal research have made Cardialysis into the successful provider of core laboratory services that it is today.

Leading experts in the field of cardiovascular imaging are supervising Cardialysis' core laboratory activities. We guarantee an independent and accurate central analysis according to the latest standards of definitions.

With the experience we have gained over the past decades we can provide excellent advice in choosing the required imaging and related logistical strategy to achieve your clinical development objectives. To date data of numerous clinical trials in which Cardialysis has been involved have been used for competent authorities (e.g FDA, EMA and CE-mark) submissions.



Guaranteed Quality

A test run is part of Cardialysis SOP ensuring high quality output. At the core laboratory the quality of the recording is assessed and feedback to the site is provided to improve quality. Every study is approved by either senior core laboratory staff or supervising cardiologists.

For all core laboratory techniques, Cardialysis provides site training and certification including acquisition guidelines, WebEx training and hands-on workshops in Rotterdam.

The quality of the Cardialysis core laboratory is guaranteed via a quality assurance system in which both inter-observer variability

and intra-observer variability are tested yearly. Reproducibility protocols including Phantom analyses are other important tools to ensure the quality of the core laboratory. Regular review of the validation of the techniques and the training of core laboratory staff complements the system.

The core laboratory techniques are validated to and in compliance with the latest International regulatory and industry standards:

ISO 14155: 2011 (GCP)

GCLP endorsed by WHO: 2009

FDA 21 CFR part 11: Electronic Records; Electronic Signatures

Data processing

Cardialysis uses an in-house state-of-the-art data processing system, which accepts both electronically or physically shipped core lab material in standard DICOM format, or specific formats such as 3D Echocardiography and Optical Coherence Tomography (OCT) materials. The system accepts virtually all-digital output of equipments from major vendors without storage restrictions.

The Cardialysis core laboratory uses validated, and vendor independent software packages, which are compatible with most commercially available imaging vendors. Output of core laboratory analysis is digitally transferred into the (eCRF) database. In agreement with the sponsor type of eCRF is predefined before the start of the study.

In-house supervising cardiologists

The Cardialysis core laboratory is supervised by leading experts in the field of cardiovascular imaging.



**Dr. Osama
Ibrahim
Soliman**

Dr. Osama Ibrahim Soliman, MD, PhD, FACC, FESC is a consultant cardiologist specialised in non-invasive cardiovascular imaging. He is leading the non-invasive imaging core laboratory at Cardialysis, Rotterdam, the Netherlands. He has over 15 years of expertise in clinical cardiology and research in medicine and cardiology. Dr. Soliman has written over 100 scientific papers in peer-review journals and book chapters. Dr. Soliman is a Fellow of the American College of Cardiology and European Society of Cardiology. He serves on the editorial board of several cardiology journals including the Journal of the American Society of Echocardiography and he is an active member of several cardiovascular working groups. Dr. Soliman has three main research areas related to non-invasive cardiovascular imaging: valvular heart disease, atherosclerosis and heart failure. Currently, he is involved in several TAVI and heart failure clinical trials.



**Dr. Yoshinobu
Onuma**

Dr. Yoshinobu Onuma, MD, PhD is a leading expert in the field of bioresorbable scaffold. He also has extensive expertise in quantitative coronary angiography (2-dimensional, 3-dimensional and dedicated bifurcation software), intravascular imaging, Syntax Score and metallic stents. He is supervising cardiologist of the angiographic core laboratory at Cardialysis.

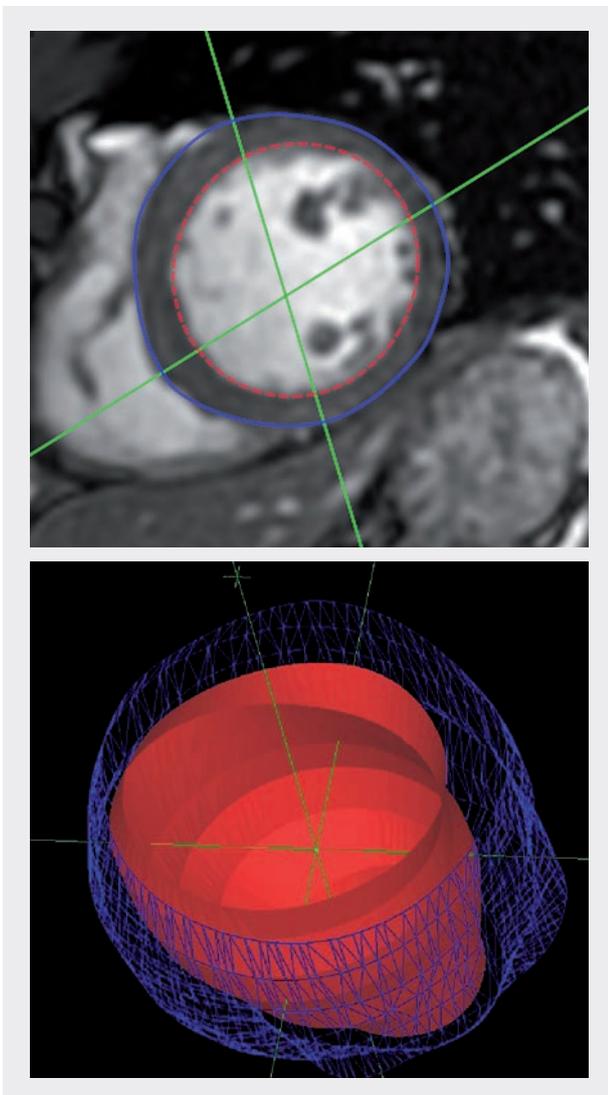
Dr. Onuma received his medical degree from Tohoku University school of Medicine in Sendai, Japan. He completed his internship and residency in internal medicine at Mitsui Memorial Hospital. He fulfilled his cardiology and interventional cardiology fellowship at the same hospital. He joined Erasmus University Rotterdam in 2007 and he was granted his doctorate in interventional cardiology in 2014. Dr. Onuma has published more than 200 manuscripts in peer-reviewed journals.



Prof. Robert-Jan M.
van Geuns

Magnetic Resonance Imaging (MRI)

Cardiac magnetic resonance imaging has grown to be a comprehensive technology to analyse the relation between left ventricular (LV) function, area-at-risk and final infarct size in the setting of acute myocardial infarction and heart failure therapies in depth.



MRI Left Ventricular analysis

Magnetic Resonance Imaging (MRI) has proven to be the most reproducible imaging modality to quantify LV function and regional systolic wall thickening. Quantitative analysis will be performed using semi-automatic software. Endo- en epicardial contours will be traced for the calculation of regional wall thickening using a 17-segment model conform the latest AHA guidelines.

With Delayed Enhanced Magnetic Resonance Imaging (DE-MRI), an image of the myocardium can be segmented to differentiate between viable and infarcted areas of muscle tissue. The non-viable area enhances intensely while normal myocardium maintains low signal intensity. The main application is investigations of improvement therapies in the treatment of acute myocardial infarction.

Provided services include expert advice in protocol design and MRI endpoints, acquisition guidelines, protocol training and certification of MRI acquisition sites, MRI data handling, independent qualitative and quantitative MRI readings.

Angiography

Angiography is the established imaging technique for coronary imaging.

Angiography is routinely used during all coronary diagnostic and interventional procedures.

Cardialysis has large experience with different types of quantitative and qualitative angiography analysis since its foundation in 1983. To date the Angiographic core laboratory has been involved in over 110 trials.

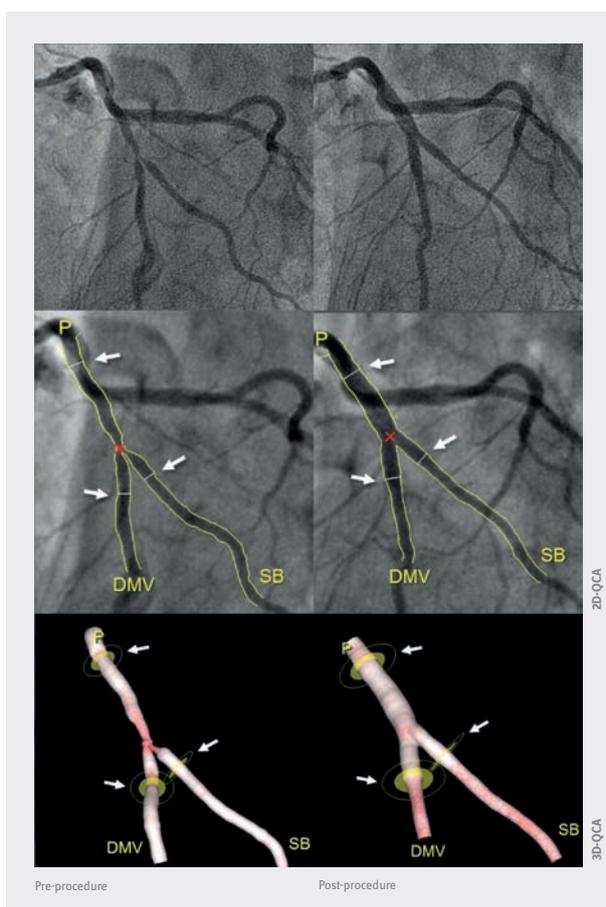
Quantitative Coronary Analysis (QCA)

QCA is a technique that provides objective and reproducible measurements of coronary artery dimensions. QCA is particularly useful for assessing the vessel lumen size, (re)occurrence of a (re-)stenosis after coronary interventions, the evaluation of mechanical interventional devices (e.g. stents) and the long term progression and regression of coronary atherosclerosis.

Bifurcation Analysis

Cardialysis holds a new approach to bifurcation analysis. As an addition to the conventional QCA analysis, a coronary bifurcation can be analysed as a single object, including the central bifurcation area together with the angulation of the bifurcation. The entire bifurcation segment can be divided in a 6-segment or in a 11-segment bifurcation model.

Besides a 2D QCA application our core laboratory is also applying 3D QCA. Out-of-plane magnification and foreshortening errors are minimized by calculating true geometric shape in 3D space from two or more 2D x-ray projections. QCA 3D offers improved analysis of difficult lesions and segment anatomy.



Supervising Cardiologists



Dr. Joost Daemen



Dr. Yoshinobu Onuma



Dr. Nicolas M.
van Mieghem

Qualitative (visual) assessment

The Angiography core laboratory has extensive experience in qualitative assessment of angiograms. The visual assessment of an angiogram may involve the analysis of morphological parameters, the coronary anatomy, the filling of coronary arteries, the cardiac function, and the evaluation of the result of an intervention according to pre-set definitions.

Myocardial Blush Grade

Myocardial blush is a measure of myocardial reperfusion in patients with acute myocardial infarction. It is estimated visually or measured using the Quantitative Blush Evaluator (QuBE).

Transcatheter Aortic Valve Implantation

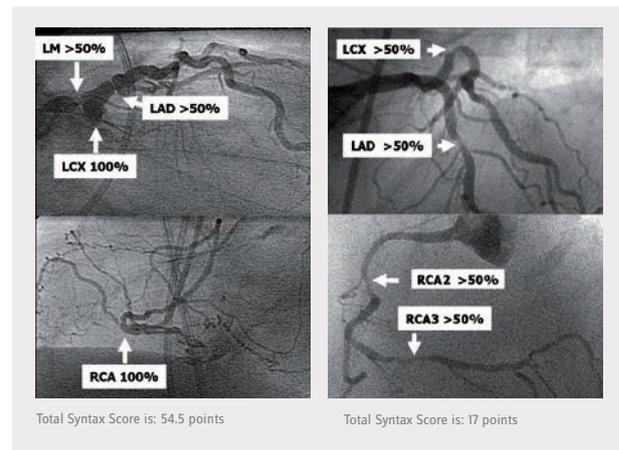
The Cardialysis core laboratory is fully geared to facilitate the industry in TAVI clinical trials. The core laboratory has gained experience in angiography analysis such as assessment of aortic regurgitation, depth of implantation and frame fracture.

Angiography Left Ventricular analysis

Left Ventricular analysis is the contour detection of the diastolic and systolic left ventricle. The difference between the diastolic and systolic state is expressed as the percentage of the ejection fraction of the left ventricle. Using software with automatic contour detection, the left ventriculograms will be analysed to assess global and regional left ventricular function, volume calculation and wall motion analysis during e.g. the procedural and follow-up studies.

SYNTAX Score

The SYNTAX Score is an angiographic tool to grade the complexity of coronary artery disease by characterising the entire coronary tree with respect to number of lesions and their functional impact, location and complexity. The SYNTAX Score can also be used to compare complexity of coronary artery disease in individual patients and entire patient cohorts. At the Cardialysis core laboratory we also apply the newly developed multislice computed tomography (MSCT) SYNTAX Score.



Intra coronary imaging

The Cardialysis Intra Coronary Imaging core laboratory has extensive experience in analysing stent studies as well as plaque progression/regression studies using classical imaging modalities such as intravascular ultrasound (IVUS). There have been numerous landmark studies in this field such as the MUSIC study, PERSPECTIVE study, IBIS 2 study, APPROACH study, ABSORB studies, RESOLUTE and LEADERS OCT substudies. To accomplish such endeavour, we have a network of more than 100 clinical sites which have been selected as our preferred choice based on their high quality performance.

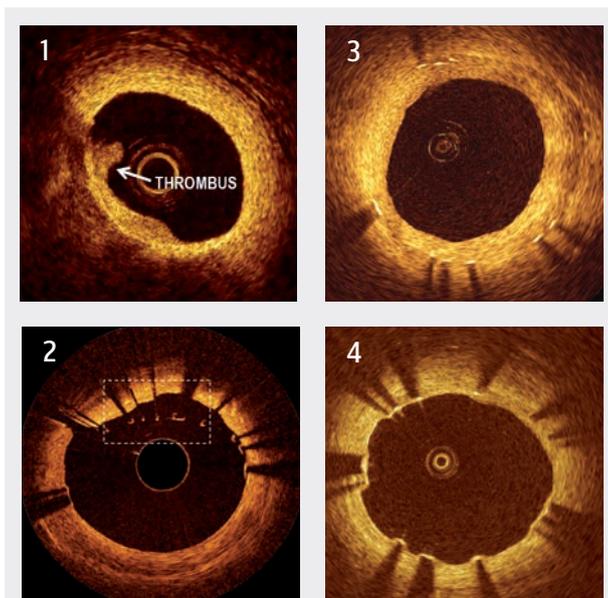


Fig 1: OCT in a native coronary artery demonstrates the presence of a lipid-rich plaque in the 6-9 o'clock position characterised by low reflectivity, speckled appearance with diffuse margins. This is covered with a bright rim of fibrous tissue corresponding to a thin-cap fibroatheroma. Mural thrombus is evident.

Fig 2: OCT immediately after stent implantation demonstrates incomplete apposition of stent struts against the vessel wall in 11-1 o'clock position.

Fig 3: OCT in a bare metal stent at 4 months follow-up visualizes individual stent struts. All stent struts are completely covered on the luminal side by a bright tissue layer. The thickness of the tissue layer ranges from 140-220 microns.

Fig 4: OCT in a drug-eluting stent at 4 months follow-up. The stent struts are covered by a bright, but very thin tissue layer. The thickness of the tissue layer ranges from 10-40 microns.

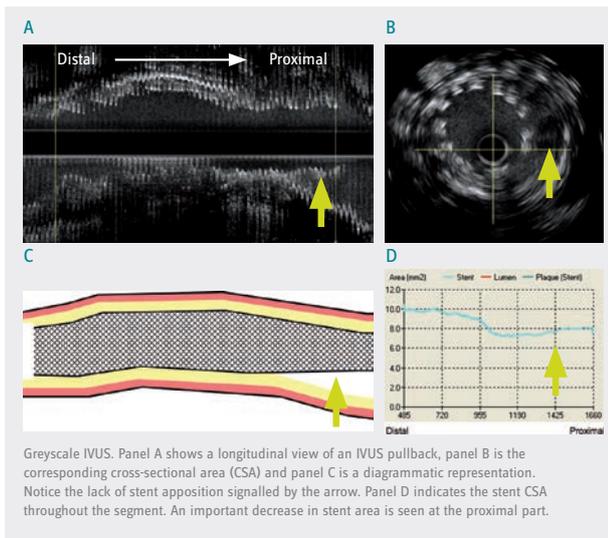
Optical Coherence Tomography

Optical Coherence Tomography (OCT) is a light-based imaging modality permitting the in-vivo visualisation of biologic tissues with an unmatched resolution of 15 microns. This unique capability has resulted in OCT being rapidly adopted and accepted in stent studies with the ability to provide accurate assessment of both stent apposition and tissue coverage over individual stent struts. Other exciting applications include the detailed assessment of the vessel wall and its structural changes over time together with the characterisation of atherosclerotic plaque components. More recently the introduction of three dimensional reconstructions has advanced this field forward. It makes our understanding of the relationship between vessel wall and coronary devices clearer and gives the opportunity to assess serially the changes in a more comprehensive manner.

Such an approach ensures that the evaluation of a particular device and/or drug will be carried out, using cutting edge technology whilst maximising the information gained from a clinical study. Closely guided by clinical experts in the specific field, Cardialysis serves as a core laboratory for a variety of these imaging techniques.

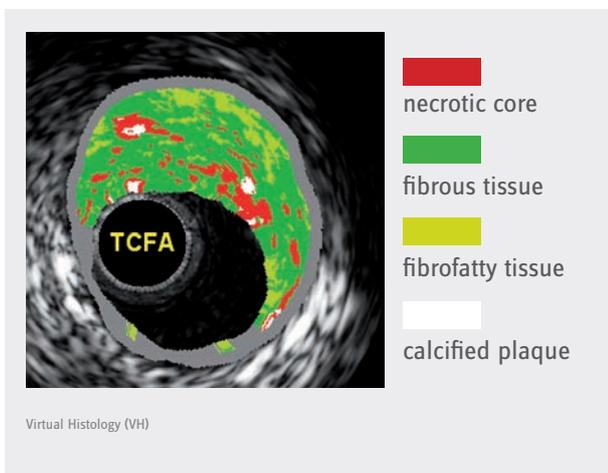


Dr. Yoshinobu Onuma



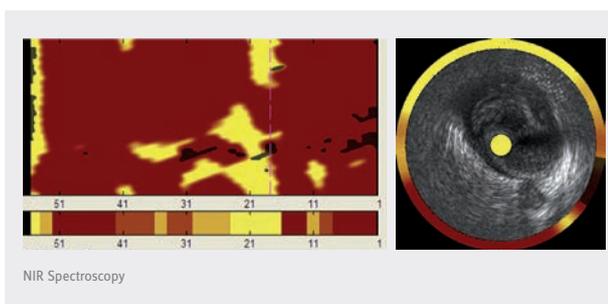
IVUS

Intravascular Ultrasound (IVUS) is a technique providing cross-sectional, high-resolution tomographic images of the arterial wall. This technique yields qualitative and quantitative assessment of the extent and severity of arterial atherosclerotic diseases. By detecting luminal, external elastic membrane and stent boundaries, IVUS is able to quantify luminal area, plaque thickness, area obstruction and quantitative and qualitative assessment of Incomplete Stent Apposition thus evaluating the results of devices and pharmaceutical treatments.



Virtual Histology

IVUS Virtual Histology is an intravascular ultrasound derived colour coded plaque characterization technique. As compared with standard IVUS, this imaging modality has the potential for more detailed assessment of different plaque components. In preliminary in vitro studies, four plaque types (fibrous tissue, fibro-fatty, necrotic core and dense calcium) as determined by histology, could be correlated with a specific spectrum of the radiofrequency signal. This technique, given its ability to identify necrotic-rich plaques, would be of great value in identifying potentially vulnerable plaque.



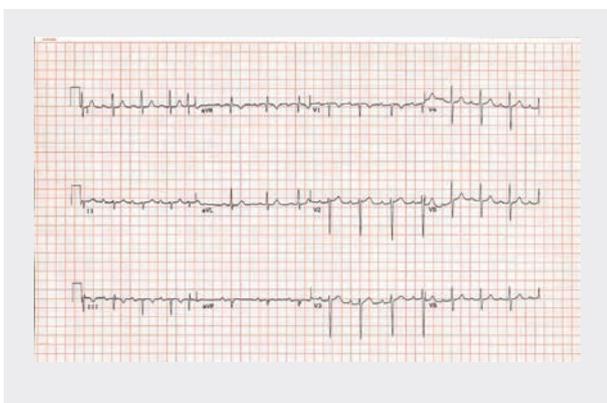
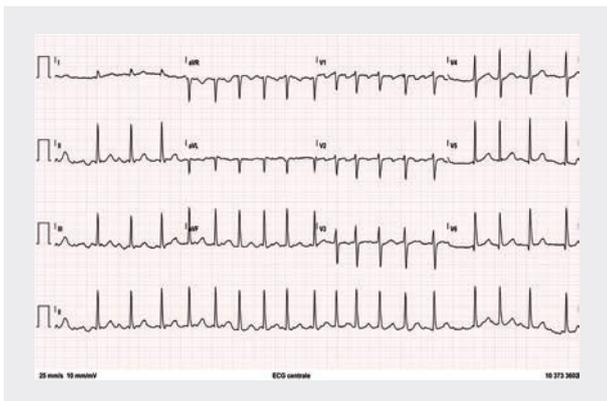
TVC Imaging System

Another imaging modality able to characterize coronary atherosclerosis (i.e. lipid core) invasively is TVC Imaging System or NIR Spectroscopy. This imaging modality is being used in the IBIS 3 trial, a study that will be able to assess the effects of rosuvastatin on the content of necrotic core (IVUS-VH) and lipid-containing regions (NIR spectroscopy) at 52 weeks.

Electrocardiography

Electrocardiography (ECG) is a widely used diagnostic tool for assessing cardiac arrhythmias, acute and prior cardiac ischaemia, and for instance left ventricular hypertrophy. Further analysis allows differentiating between physiological and pathological brady- and tachycardia, as well as changes in conduction times (QT time or bundle branch block). As such ECG continues to play an important role in many clinical trials.

Cardialysis has extensive experience with ECG analysis as it started as spin-off Holter analysis unit from the Erasmus Medical Centre in 1983. To date the Electrocardiography core laboratory has been involved in over 60 trials with more than 60.000 patients and has extensive experience in working together with different ECG monitoring device vendors.





Dr. Maarten
Witsenburg

ECG Analysis Advice and Logistics

Cardialysis provides independent electrocardiography data analysis and interpretation for cardiac arrhythmias, heart rate measurement, cardiac ischaemia and infarction. Based on our years of experience in electrocardiography we can provide you with tailor-made advice for consistent, efficient, and comprehensive ECG data collection for the purpose of endpoint adjudication. Next to that, we can advise you to select the appropriate ECG monitoring strategy.

At the ECG core laboratory interpretation and analysis is performed by well-trained in-house analysts under the supervision of a cardiologist and according to the trial protocol definitions.

We have established experience with:

ICD-analysis

We offer the possibility to analyse ICD read-outs from all companies, under supervision of a trained specialist. This offers the possibility to classify arrhythmias as they are stored in ICDs. Given the fact that ICDs are more and more used to record events, this has an important potential for clinical trials.

Holter Electrocardiography

This non-invasive tool is particularly suitable for detecting and/or monitoring cardiac arrhythmias in (ambulant) patients over time and in particular during the administration of new investigational drugs or pre or post AF ablation. In addition, Holter Electrocardiography can be used to measure cardiac rhythm, ST deviation, and QT segment interval analysis and heart rate variability.

Trans Telephonic Monitoring & Event Monitoring

Arrhythmia monitoring can be performed with the use of non-continuous ECG monitoring tools such as: trans telephonic recorders, patient and automatically activated devices, and external loop recorders. Choice of method depends on individual need and consequence of arrhythmia detection.

Implantable Loop Recorder

Continuous ECG monitoring for arrhythmia monitoring can also be facilitated with the use of implantable devices. More intensive monitoring is associated with a greater likelihood of detecting both symptomatic and asymptomatic AF.

Resting 12-lead ECG

For safety analysis in cardiac and non-cardiac trials, 12-lead ECGs are qualitatively analysed. This analysis consists of arrhythmia diagnosis, heart rate measurement and diagnosis of infarction and ischaemia. For efficacy analysis a more detailed quantitative analysis is performed in which all abnormalities are diagnosed and coded. This analysis includes the measurement of PR, QRS and QT intervals.

Exercise Tolerance Test

The exercise electrocardiogram, or ECG stress test, is used for detecting cardiac ischaemia or arrhythmias while the heart is undergoing strain imposed by a standardized exercise protocol.

Echocardiography

Cardialysis Echocardiography (ECHO) core laboratory provides adjudication of clinically validated primary and secondary endpoints in all phases of clinical trials and mechanistic insights into investigational drugs or devices. Furthermore, it provides adjudication of cardiac safety for investigational compounds.

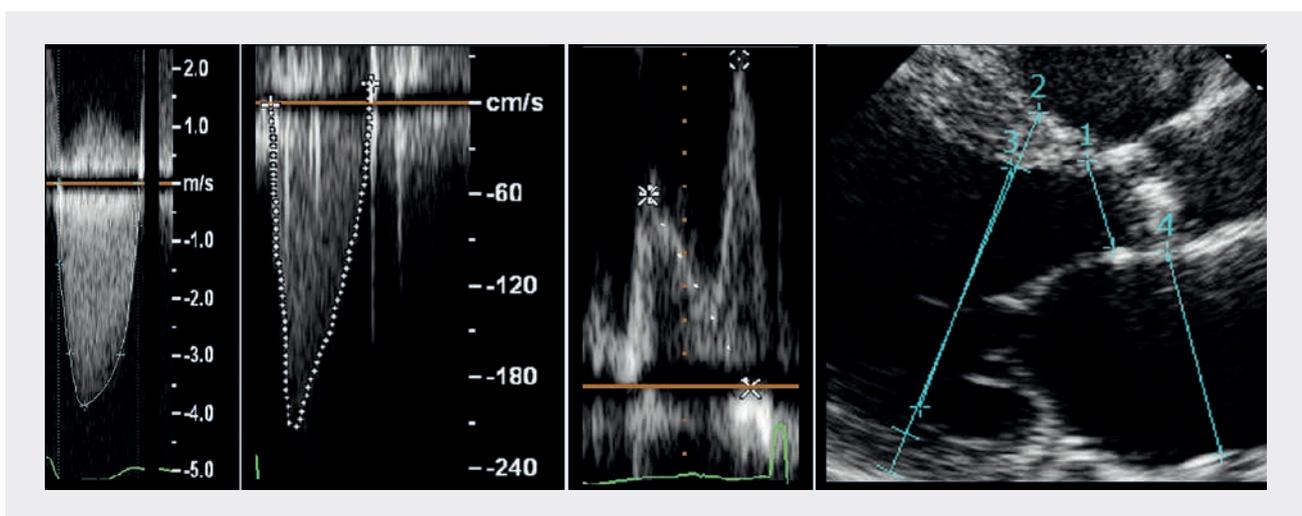
ECHO reading and analysis

Cardialysis provides central independent echo reading or analysis. Cardialysis ECHO analyses are performed by a team of senior technicians and cardiologists. Our ECHO team has extensive expertise in clinical trial design and execution. All analyses are based on the state-of-the-art American Society of Echocardiography, European Association of Cardiovascular Imaging, and Academic Research Consortium recommendations and guidelines.

Cardialysis provides analysis of Doppler, 1D, 2D, and 3D echocardiographic modalities. Currently ECHO services are in use for structural heart and heart failure clinical trials. Data from a number of these trials are used for both CE mark and FDA submissions.

ECHO Core Lab services are currently used in the following analyses:

- Percutaneous aortic valves implantation (TAVI)
- Surgical prosthetic valves replacement
- LAA occlusion devices
- Cardiac resynchronization therapy
- Heart failure investigational compounds



Supervising Cardiologists



Dr. Arend F.L. Schinkel

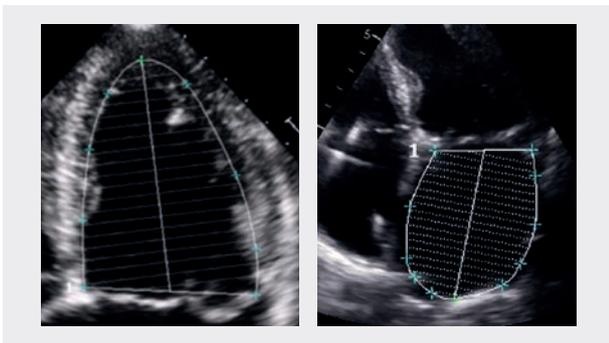


Dr. Folkert J. ten Cate



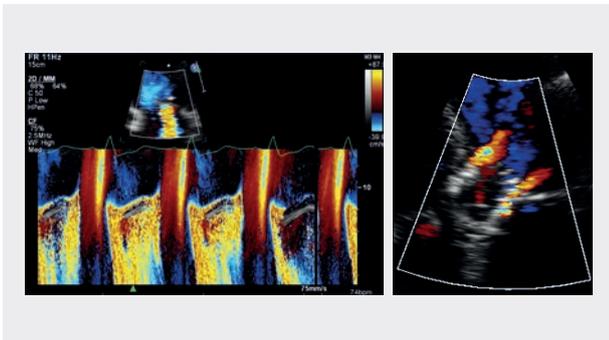
Dr. Osama I. Soliman

ECHO core laboratory provides the following analyses



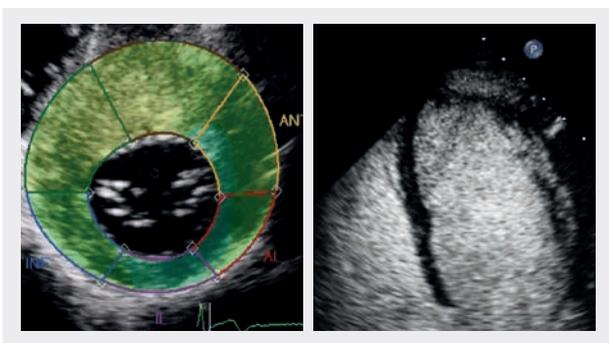
Cardiac structure and function

- 2D LV size (dimensions, areas, and volumes)
- 2D LV ejection fraction
- 2D & M-mode assessment of LV mass
- 2D LV regional wall motion
- 2D assessment of left atrial size, function



Physiologic and hemodynamic assessment

- Doppler comprehensive hemodynamic assessments
- Quantification of mitral regurgitation
- Quantification of aortic regurgitation
- Quantification of pulmonary regurgitation
- Quantification of tricuspid regurgitation
- 2D stress echocardiography & contractile reserve
- Tissue Doppler quantitative myocardial function



Together with our industry partners, we are developing

vendor independent

techniques for the following

core laboratory services:

- 2D speckle-tracking deformation imaging
- 3D LV volumes & EF
- 3D RV volumes & EF (vendor independent)
- 3D aortic and mitral regurgitation
- Contrast echocardiography (perfusion/wall motion)



Dr. Koen Nieman

MultiSlice Computed Tomography

Plaque and Stenosis Imaging

Over the past decade cardiac Computed Tomography (CT) has developed into a valuable cardiac imaging tool. CT imaging of the coronary arteries allows for non-invasive assessment of coronary atherosclerosis and narrowing of the coronary lumen. Quantitative tools are available to measure the lumen dimensions as well as the volume of atherosclerotic plaque. Cardiac CT can further be employed to assess coronary bypass grafts and certain types of coronary stents/scaffolds.

Non-coronary applications and Valve Analysis

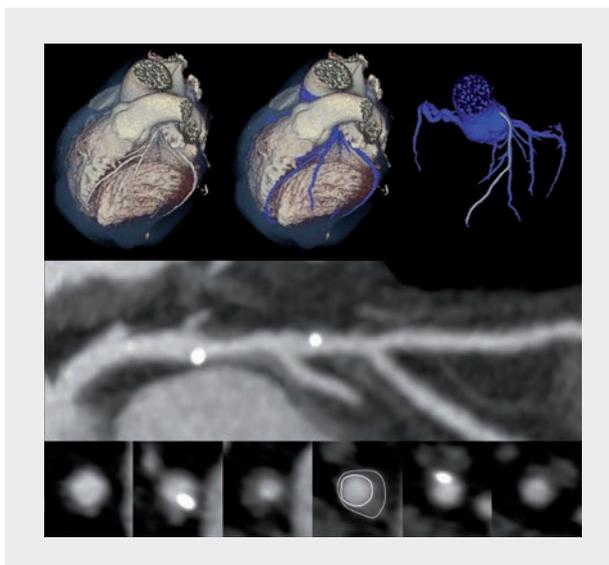
Non-coronary applications of cardiac CT include quantification of contractile ventricular function, and more recently developed techniques such as myocardial perfusion and late myocardial enhancement imaging. Cardiac CT has excellent three-dimensional spatial resolution and offers unmatched structural assessment of the heart, i.e. the left atrium and its appendage, the pulmonary and cardiac veins or valves.

Prior to percutaneous valve interventions, cardiac CT can display the anatomy and dimensions of the left ventricular outflow tract, important for procedure preparation and selection of the type and size of the devices. In addition peripheral vascular access routes may be assessed by CT.

CT SYNTAX

The Syntax Score is an angiographic tool to grade the complexity of coronary artery disease by characterising the entire coronary tree with respect to number of lesions and their functional impact, location and complexity. The Syntax Score can also be used to compare complexity of coronary artery disease in individual patients and entire patient cohorts. At the Cardialysis Core Lab we also apply the newly developed multislice computed tomography (MSCT) Syntax Score.

Projects involve quantitative CT angiographic follow-up after percutaneous coronary interventions, monitoring of bypass graft patency and pre-TAVI evaluations. Provided services include trial design and CT endpoints, acquisition guidelines, web-based training and certification of CT acquisition sites, CT data handling, independent qualitative and quantitative CT readings.



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