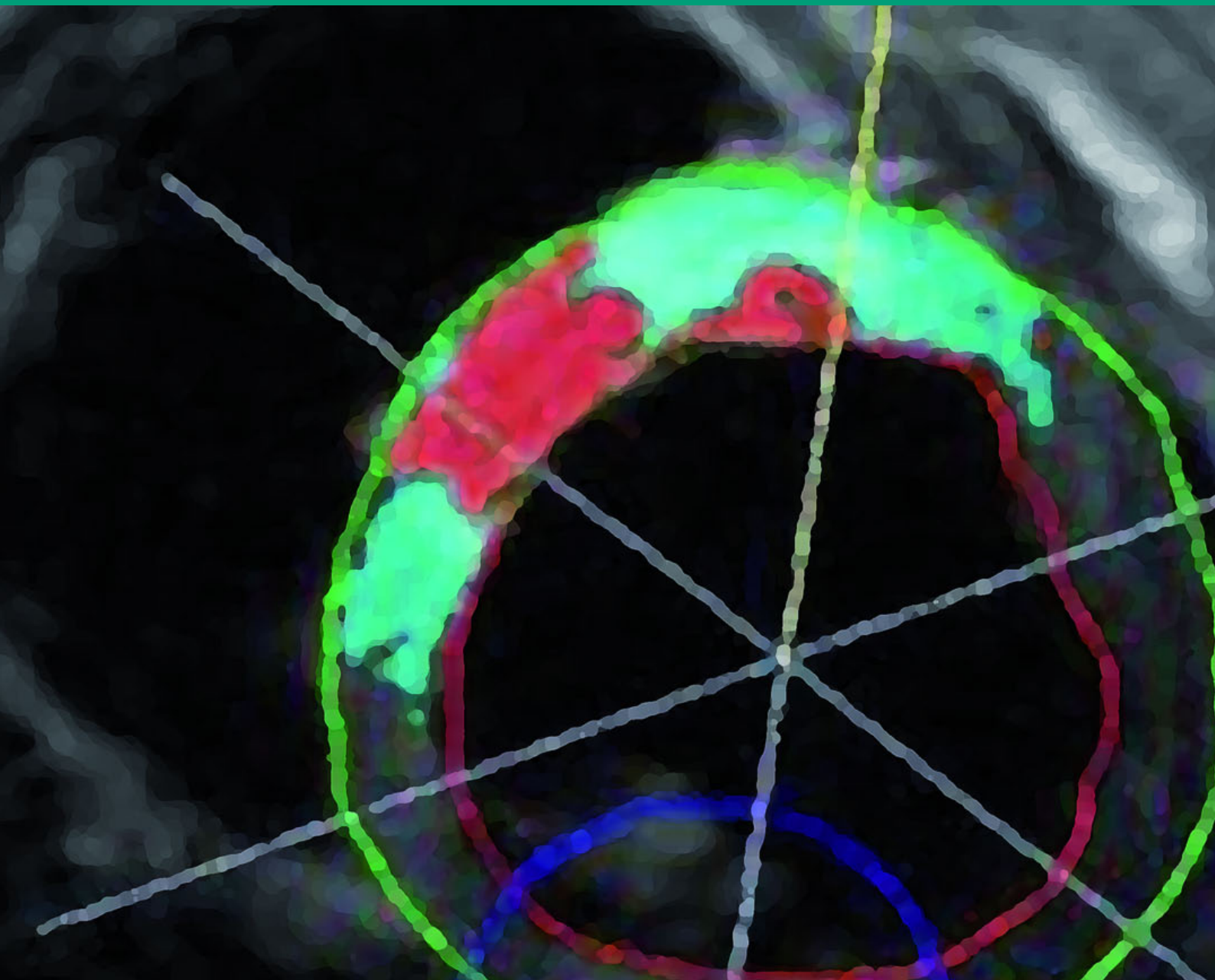
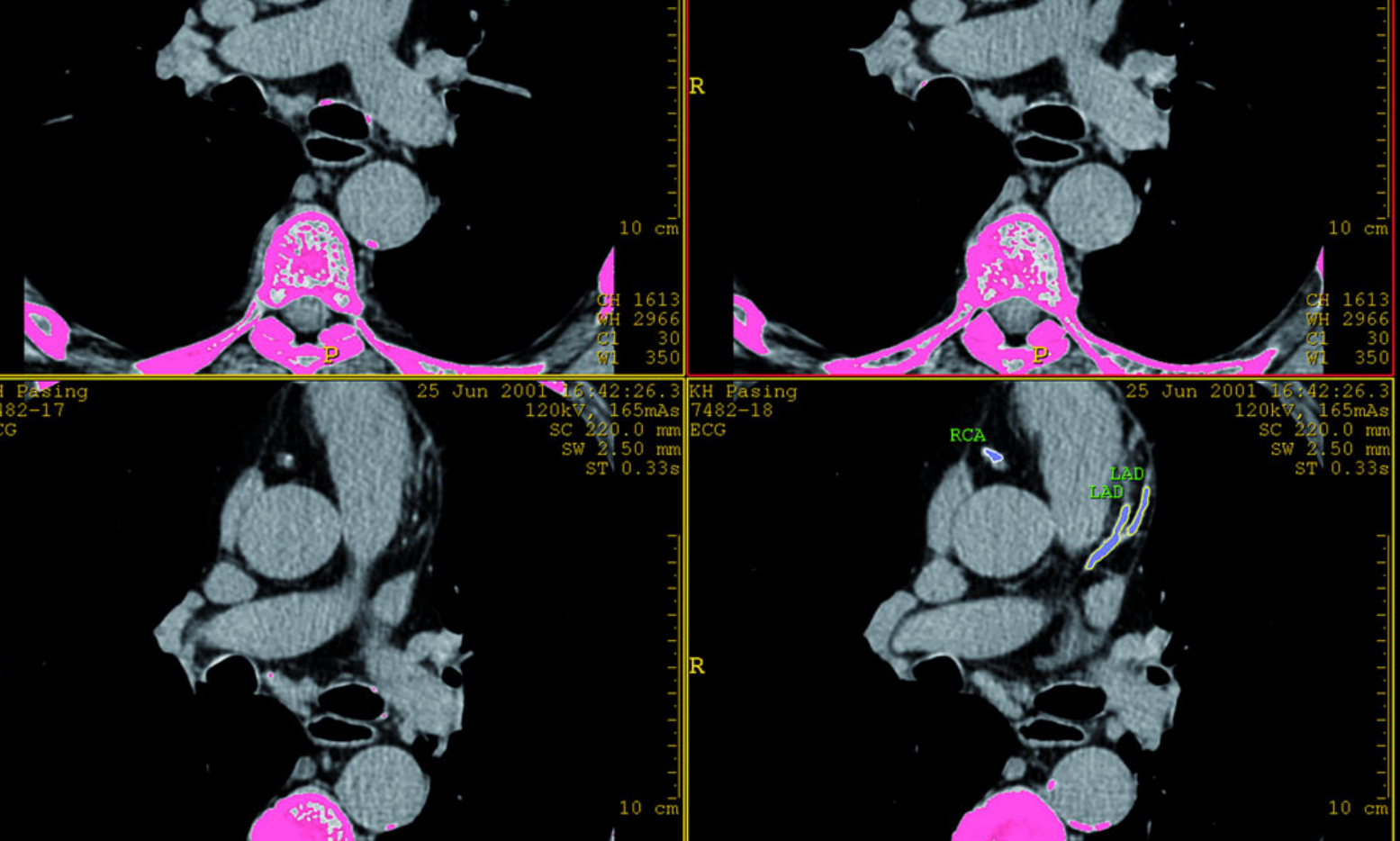


Applied Research Departments

Multi-Departmental Clinical Projects





Applied Research Departments

Cardiovascular Translational Research

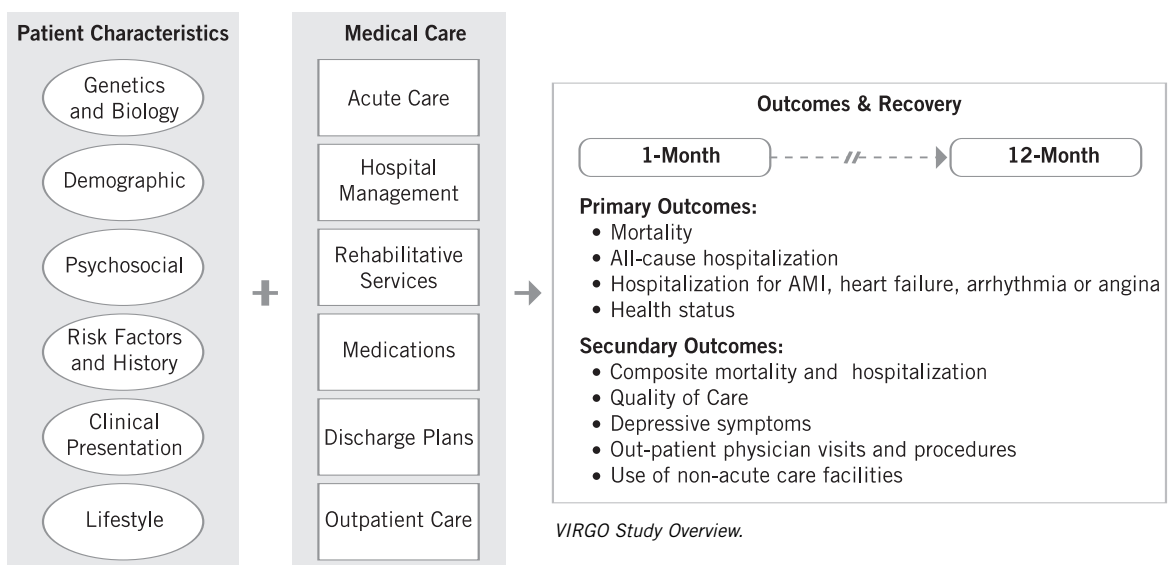
Atherosclerosis is the underlying cause of most cardiovascular disease, the leading cause of death worldwide. Atherosclerotic disease progressively damages vital organs and vascular areas, leading to clinical conditions such as peripheral vascular disease, myocardial infarction and stroke. Aside from the human cost, atherosclerotic disease also incurs a high economic cost. Atherosclerotic lesions evolve subclinically over several decades, and diagnosis is currently only possible once these catastrophic conditions have already appeared. The CNIC's main efforts in applied research are therefore aimed at improving diagnosis through the use of the latest imaging technologies and at testing the efficacy of new treatments.

IMJOVEN Study

Although heart disease in young women causes many deaths, it has been virtually ignored by the medical profession because it represents only a small fraction of the total incidence of atherosclerotic heart disease. However, young women who suffer an acute myocardial infarction (AMI) have a mortality risk markedly higher than that of young men, and the limited data on young women from minority groups in the USA suggest that this population may have the highest risk of any young subgroup. There have been no large, prospective studies of ischemic heart disease in young women, even though the death toll is comparable to that due to breast cancer. Findings from the small number of studies that have been published suggest that the biology, epidemiology, care, and outcomes of heart disease in women differ from those of men. The IMJOVEN study is the Spanish counterpart of the VIRGO study, an NIH-sponsored investigation led by Harlan Krumholz of Yale University into the excess risk in young women with AMI.

The specific aims of VIRGO and IMJOVEN are as follows. 1) To characterize sex differences after hospitalization for AMI for a broad range of outcomes including mortality, all-cause readmission, rehospitalization for cardiovascular causes, and adverse health status. 2) To evaluate the influence of demographic, clinical, metabolic, biochemical, genetic, psychosocial, and lifestyle factors on outcomes for young women and men with AMI and to examine whether sex-based variation in these factors is associated with variation in outcomes. 3) To compare the clinical treatment of young men and women who present at hospital with AMI and determine whether differences in quality of care may be associated with differences in outcome. 4) To describe the relationship of female-specific factors—including genetic variants, sex hormones, reproductive history, prior use of estrogens and menstrual cycle history—with disease outcomes for women. 5) To develop comprehensive prognostic scores to stratify risk in this young population and identify predictors of early (within 1 month of discharge) and longer-term (1 year) outcomes. 6) To create a blood and DNA repository as a resource for future studies. 7) To partner with national and international organizations to disseminate study findings in order to improve the prevention, care, and outcomes for young patients with AMI.

Our aim with IMJOVEN is to study 450 patients (300 women and 150 men) with a previous history of AMI, using the same protocol as the VIRGO study. We have already recruited 395 patients in 24 hospitals in Spain, and we are well on our way to completing recruitment on schedule. IMJOVEN is coordinated by the Department of Translational Research at the CNIC, the Spanish Society of Cardiology and the RECAVA and Heracles networks. Funding comes from a FIS grant, the NIH and the CNIC.



AWHS



The Aragon Workers Health Study (AWHS) is being conducted in collaboration with the Instituto Aragonés de Ciencias de la Salud (IACS) and the General Motors factory in Zaragoza. The study examines the development of cardiovascular disease and its risk factors by monitoring factory workers at their annual medical checkups. AWHS is an open cohort study including more than 5000 workers. During 2010, study participants underwent a standardized clinical exam, laboratory assays, and collection of biological samples including serum, plasma, whole blood, urine and DNA.

A medical imaging facility has been established to allow further exploration of the presence of subclinical atherosclerosis in these participants. Over the next three years, participants will be examined for TC calcium score, 3D ultrasound of carotid arteries and abdominal aorta, and ankle-brachial index. All laboratory procedures have been reviewed and improved to meet the ISO 9001:2008 standard, verified by an external audit.

The study is financed by the Departamento de Salud y Consumo of the Aragon regional government and the CNIC. In addition, external funding has been raised for the following sub-studies on the cohort, which are being conducted by CNIC-based researchers: "Insulin resistance and inflammatory response to oxidative stress: Study of determinants and interactions" (ISCIH CPO8/112); "Identification of the genetic determinants of mitochondrial DNA content in a working population, and its relationship with oxidative stress and subclinical atherosclerosis" (ISCIH PI10/21); "Cadmium exposure, metallothionein levels, and kidney disease in a general motors company assembly plant" (Johns Hopkins NIOSH Education and Research Center Research Project Award); and "DNA methylation and the association of cadmium exposure with chronic kidney disease in a population-based occupational study" (Johns Hopkins NIEHS).

PESA, CNIC- Santander

PROGRESSION OF EARLY SUBCLINICAL ATHEROSCLEROSIS, CNIC-SANTANDER

Strategies to identify individuals with subclinical alterations indicating increased risk of cardiovascular disease have been boosted by the recent development of advanced non-invasive imaging techniques (magnetic resonance imaging, positron emission tomography, and computerized tomography) that can be applied to large populations. Several studies currently underway, such as the High-Risk Population (HRP) study, led by Valentín Fuster in the USA, are pioneering the application of these techniques to population studies. However, most studies to date have examined populations over the age of 60. Atherosclerotic disease in this group has already had several decades of evolution and may not be fully reversible. To assess the early onset of atherosclerosis, longitudinal vascular imaging studies are needed to provide information about middle-aged populations.

PESA is a longitudinal study, run in partnership with Banco Santander and the Marcelino Botín Foundation, into the use of imaging techniques to detect the prevalence and rate of progression of subclinical vascular lesions in a population of 4500 male and female workers aged between 40 and 54 years. The study examines the association of these clinical parameters with the presence of genetic, epigenetic, metabolomic, proteomic and environmental factors, including dietary habits, physical activity, biorhythms, psychosocial characteristics and exposure to environmental pollutants.

Participants are first assessed with basic imaging techniques, including CT imaging to estimate coronary calcium, 3D ultrasound of carotid artery, and 2D ultrasound measurement of abdominal aorta and the rate of ankle-brachial pressure. These techniques are used for the early diagnosis of individuals with subclinical atherosclerosis. Participants are then studied with two advanced imaging techniques: magnetic resonance imaging (MRI) and positron emission tomography (PET). These advanced techniques will help determine participants' atherosclerotic burden and monitor its progression and the presence and progression of inflammation in atherosclerotic plaques.

The study will also provide important information about the prevalence of unrecognized myocardial infarction in this population, and will assess the prevalence and progression of subclinical atherosclerosis in women during perimenopause and its relation to cardiovascular risk factors and hormonal changes.

The PESA CNIC-Santander study will help to identify risk factors and daily habits that influence the development of atherosclerosis, and will improve the prevention of atherosclerotic disease by achieving early diagnosis before the appearance of symptoms.

Polypill/FOCUS

The prevention of cardiovascular disease is hampered by several factors, including wide variability in the pattern of prescription among physicians, limited access to expensive drugs in emerging countries, and poor adherence to medication. The use of fixed dose drug combinations (polypill) has been recommended to improve accessibility and adherence to treatment. The CNIC, working in a private-public partnership with Ferrer International, has devised a fixed dose combination for secondary prevention. The CNIC-Ferrer polypill project is led by Valentín Fuster and is coordinated by the Translational Research Department.

During the last year we have conducted several clinical trials to ensure the quality and safety of the polypill. A new study to explore the potential pharmacodynamic interactions with simvastatin was launched in Spain. The kick-off meeting of the FOCUS project, which tests the fixed-dose combination concept for cardiovascular prevention in populations with different socio-economic characteristics, was held in Madrid last June. Patient recruitment will begin during the first half of 2011. An important aim of FOCUS is to understand the factors that determine poor treatment adherence and inappropriate prescribing for secondary cardiovascular prevention. This will allow FOCUS to establish recommendations for better use of medication in patients with ischemic heart disease. After the successful completion of FOCUS, secondary prevention medication will be available and affordable for large numbers of patients in developed and developing countries. The CNIC's partners in the FOCUS consortium are the Mario Negri Institute (Milan), the Fundación Ruscalleda (Buenos Aires), the Fundació Clinic (Barcelona), Ferrer Internacional (Barcelona), the Agencia Española de Evaluación de Tecnologías Sanitarias, the Instituto de Salud Carlos III (Madrid), the World Heart Federation (Geneva) and the Federación Argentina de Cardiología (Buenos Aires).

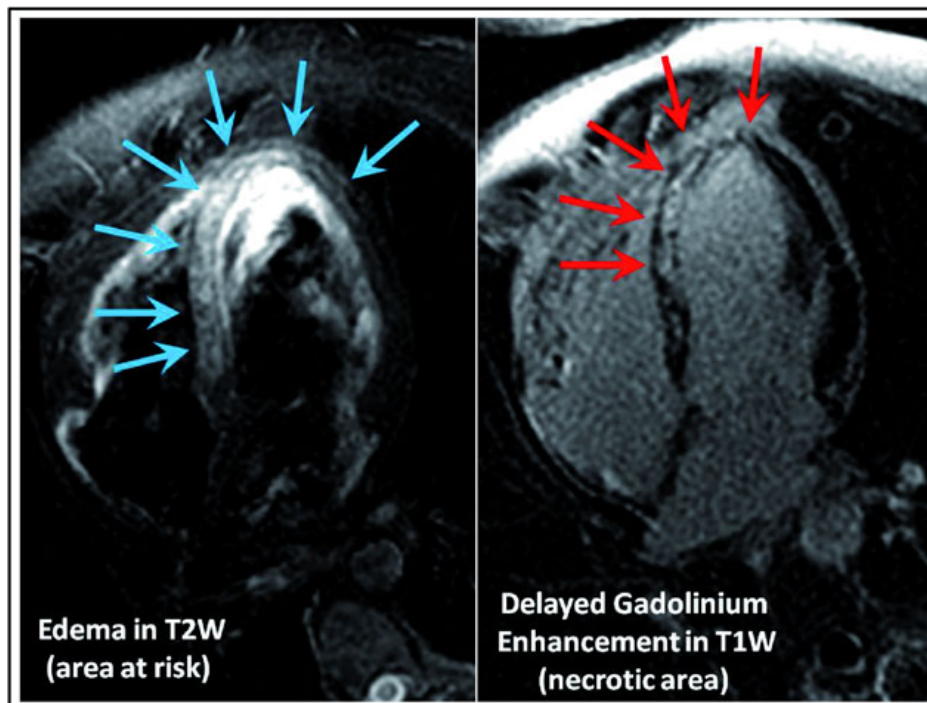
METOCARD-CNIC

Acute myocardial infarction (AMI) is the main cause of death in western countries. The best strategy to limit myocardial damage is to perform an early coronary reperfusion; however, reperfusion itself comes at the price of additional myocardial damage, known as ischemia/reperfusion injury (I/R).

The duration of ischemia can only be shortened through coordinated healthcare policies aimed at early detection and transfer of patients to hospitals with angioplasty capabilities. I/R injury, on the other hand, could potentially be reduced by pharmacological approaches; but despite great efforts, no therapy has been shown to consistently limit this phenomenon.

β -blockers are a class of drugs that have been used to treat cardiovascular conditions for several decades. β -blockers reduce mortality when administered after an AMI, and are a class IA indication in this context. What remains unclear is what timing and route of β -blocker administration gives the maximum cardioprotective effect. In particular, whether early β -blocker administration is able to reduce infarct size is a subject of debate. Experimental data from our laboratory suggest that the β_1 selective blocker metoprolol is able to limit the area of necrosis only when administered before reperfusion.

METOCARD-CNIC is a multicenter randomized clinical trial comparing the effect of early and delayed metoprolol initiation on infarct size and clinical events in more than 200 patients with AMI. Patients are currently being recruited in cities across Spain in close collaboration with emergency medical services and hospitals. The main endpoints of this trial will be evaluated by innovative magnetic resonance imaging protocols developed at the CNIC Imaging Facility.



Imaging of human heart after an acute myocardial infarction.

Apical four chamber view of a human heart six days after an acute myocardial infarction. Left panel depicts edema (without contrast infusion). Arrows delineate the at-risk area of the left ventricle. Right panel shows the necrosed area (after Gadolinium contrast injection). Arrows delineate the necrotic area of the left ventricle. Note that the at-risk area is larger than the necrotic area, providing evidence of cardioprotected areas (areas at risk but with no necrosis). (Picture provided by Gonzalo Pizarro, Leticia Fernández-Friera et al., unpublished data.)

**METOCARD-CNIC team:**

- Borja Ibáñez, (PI)
- Valentín Fuster, Carlos Macaya, Jesús Jiménez-Borreguero (Co-PIs)

Other relevant investigators:

- Gonzalo Pizarro, Leticia Fernández Frieria, Luz Álvarez (CNIC)
- A complete list of investigators can be found in www.metocard.es