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**Author:** Nucifora, Gaetano  
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Chapter 1

General Introduction and Outline of the Thesis
GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Identification of patients at risk of developing coronary artery disease events is one of the most challenging issues in clinical cardiology. The risk of acute coronary events in subjects without known coronary artery disease is related to the presence of cardiovascular risk factors. Several scoring tools that include demographic and clinical characteristics have been developed and are frequently used in clinical practice to predict the 10-year risk of hard coronary events. These tools allow stratification of patients into low-, intermediate, and high-risk categories, in order to determine the need and intensity of risk-modifying interventions.\textsuperscript{1-3}

However, traditional risk assessment may still fail to identify a considerable proportion of patients with future coronary events, since it provides a statistical probability of having coronary artery disease rather than a direct individual assessment.\textsuperscript{4} Indeed, it has been observed that as much as 20% of acute coronary events can occur in the absence of major cardiovascular risk factors.\textsuperscript{5}

The potential value of additional risk assessment with stress testing (i.e. electrocardiographic exercise test, stress echocardiography or myocardial perfusion imaging) to improve the identification of patients at risk of coronary events has been extensively evaluated.\textsuperscript{6,7} More recently, direct visualization of subclinical atherosclerosis, by coronary artery calcium score (CACS) assessment with electron-beam computed tomography (EBCT) or multi-slice computed tomography (MSCT), and MSCT coronary angiography, has emerged as an extremely rapidly developing non-invasive imaging modality to refine traditional risk assessment. These imaging techniques may be a practical approach since they provide a direct non-invasive estimate of atherosclerotic plaque burden in the coronary arteries (Figure 1).\textsuperscript{8} The application of these imaging modalities may be particularly useful among patients with history of atrial fibrillation, since coronary artery disease is considered to be highly prevalent in
patients with atrial fibrillation and may be one of its potential etiologic factors.\textsuperscript{9}

**Figure 1. Panel A.** Evaluation of CACS by MSCT reveals the presence of coronary calcium in the left anterior descending coronary artery. **Panel B.** Curved multi-planar reconstructions showing three distinct plaque characteristics observed on MSCT with non-calcified plaque (arrow, left panel), mixed plaque (arrow, mid-panel), and calcified plaque (arrow, right panel).

Conventional echocardiography as well as novel echocardiographic techniques, such as speckletracking echocardiography, may be of value as well for the identification of patients with obstructive coronary artery disease. Comprehensive echocardiographic assessment of cardiac and ascending aorta calcifications, which have been related to coronary artery disease and cardiovascular events,\textsuperscript{10,11} may be a simple, non-invasive, and widely available technique to predict the presence of extensive coronary calcium and obstructive coronary artery disease (Figure 2).

Speckle-tracking echocardiography, a novel non-invasive imaging modality able to quantify myocardial motion and deformation in a regionby-region analysis, may detect the presence of subclinical impairment of myocardial function, which could represent a marker of obstructive coronary artery disease (Figure 3).\textsuperscript{12}

Advanced echocardiographic imaging techniques may be of incremental diagnostic and prognostic value among patients with clinically overt cardiac diseases; contrast-enhanced echocardiography, real-time three-dimensional echocardiography (RT3DE) and speckle-tracking imaging have indeed demonstrated their incremental value over conventional echocardiography for the assessment of global and regional left
ventricular function and for a better understand of cardiac mechanics.\textsuperscript{13-15} The use of contrast agents allows for the evaluation of cardiac flow dynamics, which are closely related to myocardial motion and deformation, \textsuperscript{16,17} and of myocardial blood flow.\textsuperscript{18}

\textbf{Figure 2.} Example of a 50-year-old male with calcified posterior mitral annulus and aortic valve and 3-vessel coronary artery disease. Panel A shows the parasternal long-axis view of the left ventricle with calcification of the aortic valve (arrows) and the posterior annulus of the mitral valve (arrow). Panel B shows the apical long-axis view of the left ventricle and calcified posterior mitral annulus (arrow). Panel C shows the right coronary artery with a significant lesion of the mid segment (arrow) and panel D shows the left coronary system with significant lesions in the circumflex coronary artery and first diagonal branch of the left anterior descending coronary artery (arrows).
Figure 3. Speckle-tracking echocardiography provides a direct measure of myocardial deformation and can therefore be used to detect subtle abnormalities in LV systolic and diastolic function. Global longitudinal strain and strain rate curves obtained by speckle-tracking analysis from an apical 4-chamber view are shown in panel A and B, respectively.

**Coronary artery calcium scoring and multi-slice computed tomography coronary angiography**

EBCT and MSCT have been previously validated as sensitive techniques for the detection of coronary calcium, a marker of coronary atherosclerosis.\(^{19}\) EBCT was introduced in the early 1980s specifically for cardiac imaging. The use of non-mechanical X-ray source allows for prospective ECG-triggered image acquisition with high temporal resolution (50–100 ms), thereby limiting respiratory and cardiac motion artifacts. Coronary calcifications are defined as hyper-attenuating lesions >130 Hounsfield units with an area of three or more adjacent pixels (at least 1 mm\(^2\)).\(^{20}\) To quantify the extent of coronary calcium, a score has been developed by Agatston et al.\(^{21}\) To express the extent of detected coronary calcium, CACS is commonly classified into four categories: 0, 1–99, 100–399, and ≥400, indicating no calcific deposits, mild, moderate, and severe coronary calcifications, respectively.\(^{22}\) Several studies have recently demonstrated that CACS obtained using newer generation MSCT scanners (with higher number of detectors and faster X-ray gantry rotation time) are comparable to those obtained with EBCT.\(^{23}\)
Main disadvantages of calcium scoring are the lack of information on the degree of coronary stenosis and the inability to identify non-calcified plaques. The introduction of MSCT coronary angiography has overcome these limitations, allowing direct non-invasive anatomic assessment of the coronary arteries. For diagnosis, numerous studies support the use of MSCT coronary angiography for rule out of the presence of coronary artery disease with a high accuracy;\textsuperscript{24,25} a differentiation can also be made between non-calcified plaques having low attenuation, calcified plaques with high attenuation, and mixed plaques with both non-calcified and calcified elements (Figure 1).\textsuperscript{26} Furthermore, plaque remodelling, a marker of vulnerability, can also be appreciated.\textsuperscript{26} These advantages have led to an increased use of MSCT as a gatekeeper for further diagnostic testing. In addition, early identification of coronary artery disease with MSCT coronary angiography may be useful for risk stratification.\textsuperscript{27}

**Echocardiographic assessment of cardiac and ascending aorta calcifications**

Previous studies have consistently demonstrated that mitral annular calcium and aortic valve sclerosis are not simple passive degenerative disorders influenced by mechanical stress, but active inflammatory processes with histopathologic features similar to atherosclerosis.\textsuperscript{28} Large population cohort studies have also shown that aortic valve sclerosis and mitral annular calcium are associated with increased cardiovascular morbidity and mortality.\textsuperscript{10,11} Because it is unlikely that aortic valve sclerosis and mitral annular calcium directly lead to adverse cardiovascular outcomes, their relation with coronary atherosclerosis most likely explains these observations. Accordingly, echocardiographic recognition of cardiac and ascending aorta calcium could be helpful to optimize the identification of patients with obstructive coronary artery disease.
Echocardiographic assessment of myocardial deformation
Speckle-tracking echocardiography has been introduced in the last years for the assessment of myocardial deformation; it allows an angle-independent analysis of myocardial strain (and strain rate) in multiple directions (radial, longitudinal and circumferential), through the detection and tracking of the unique myocardial ultrasound patterns frame by frame. The in-plane frame-to-frame displacement of each pattern over time is used to derive strain.\textsuperscript{29} Using this technique, regional and global myocardial contractility can be studied, as well as more complex cardiac mechanics, such as the systolic twisting motion of the left ventricle along its longitudinal axis, which results from the opposite rotation of the left ventricular apex compared with the base. Left ventricular twist has emerged as an important, sensitive parameter of left ventricular systolic function.\textsuperscript{30}

Real-time three-dimensional echocardiography
Over the last few decades, advances in ultrasound and computer technologies have enabled on-line real-time display of three-dimensional (3D) images of the heart. Several studies have demonstrated superior accuracy and reproducibility of RT3DE over standard two-dimensional echocardiography for quantification of left ventricular size and function.\textsuperscript{31} In addition, the 3D tracking of endocardial motion of volumetric segments refines the analysis of regional left ventricular function and allows the assessment of temporal sequence of regional myocardial contraction, thus providing quantitative data of left ventricular dyssynchrony.\textsuperscript{31} In patients with acute myocardial infarction (AMI), the presence of significant left ventricular dyssynchrony has been associated with adverse left ventricular remodelling and functional impairment at follow-up.

Contrast-enhanced echocardiography
Transthoracic echocardiography (and in particular RT3DE) is not able to provide diagnostically useful images in a non-negligible proportion of
patients, mainly because of obesity and lung disease. The use of echo-contrast agents solves these issues, providing cardiac chamber opacification and improving endocardial border definition, thereby allowing a more accurate quantification of left ventricular function (Figure 4).

Figure 4. Panel A. Example of fair-quality echocardiogram during nonenhanced RT3DE. Panel B. Optimal LV chamber opacification and improved endocardial border definition during contrast-enhanced RT3DE in the same patient. The 3 apical views are shown with the 4-chamber view as a reference view in the top right and the 2- and 3-chamber views in the bottom left and bottom right, respectively. Top left: short-axis view.

Besides improving the assessment of left ventricular function, echo-contrast agents may also be used to assess myocardial perfusion and to investigate left ventricular hydrodynamics. During early left ventricular filling, the blood flow forms an intraventricular rotational body of fluid, which is critical in optimizing the blood flow during systole. Knowledge of abnormalities involving left ventricular hydrodynamics may be useful, since it provides direct information regarding the ultimate goal of left ventricular performance, i.e. optimal blood flow.
OBJECTIVES AND OUTLINE OF THE THESIS

The objectives of the thesis were to investigate the incremental value in clinical practice of different non-invasive imaging techniques in patients with suspected coronary artery disease and in patients with acute myocardial infarction (AMI).

In Part I, the use of non-invasive imaging modalities for diagnosis and risk stratification of patients with suspected coronary artery disease will be introduced. An overview of the prognostic value of CACS assessment is provided in Chapter 2; in addition, potential other applications of CACS assessment and the limitations of the technique are discussed. The incremental value of CACS and MSCT coronary angiography and the relation between coronary atherosclerosis and presence of abnormal stress testing are subsequently investigated in the general population (Chapters 3-4) and among patients with paroxysmal or persistent AF (Chapters 5-6). The clinical usefulness of comprehensive echocardiographic assessment of the burden of cardiac and ascending aorta calcium to predict coronary artery calcium and presence and severity of obstructive coronary artery disease is evaluated in Chapter 7 while in Chapter 8 the relation between obstructive coronary artery disease and subclinical left ventricular systolic dysfunction, as assessed by speckle-tracking echocardiography, is investigated.

Part II will discuss the diagnostic and prognostic value of novel echocardiographic techniques in patients with AMI. The incremental value of contrast-enhanced RT3DE early after AMI was investigated in Chapter 9. The left ventricular hydrodynamics early after AMI and their relation to left ventricular diastolic function and infarct size are evaluated in Chapter 10, while the effects of AMI on left ventricular torsional mechanics and on left ventricular dyssynchrony are investigated in Chapters 11-13.
REFERENCES


