Examine Thy Heart With All Diligence
Evaluation of Cardiac Function Using Fast Computed Tomography

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Cardiovascular disease is a major cause of mortality in Western society but at its early phase may manifest as subtle alterations in coronary epicardial or microvascular function, including endothelial dysfunction, abnormal perfusion or permeability, and remodeling, which may precede clinical manifestation of vascular disease. These modifications might be associated with subclinical decline in diastolic and/or systolic function and left ventricular (LV) remodeling. Evaluation of myocardial perfusion and microvascular function to identify areas of persistent ischemia or hibernating myocardium, endothelial, or LV dysfunction is, therefore, important for clinical decision-making and fuels the search for noninvasive techniques assessing different stages of cardiac disease.

Several noninvasive or minimally invasive techniques currently used to explore cardiac function, such as echocardiography, scintigraphy, and single-photon emission computed tomography, show diagnostic reliability but low spatial resolution and poor anatomic details. Therefore, higher-resolution techniques, like positron emission tomography, MRI, and computed tomography (CT), have been steadily gaining popularity. MRI can assess cardiac function, mass, volume, and myocardial viability, with limited application in patients with metal fragments, and positron emission tomography provides reliable estimates of myocardial perfusion and metabolism, albeit at low spatial resolution. Furthermore, since its inception in the 1970s, CT quickly incorporated into clinical practice, and recent technical advances have placed it in the forefront for comprehensive evaluation of cardiac function at several levels, from the function of the heart as a pump, to the behavior of the microvessels that feed its walls (Figure 1). For example, CT overcomes some of the limitations of MRI, because it can study patients with defibrillators or pacemakers, has a shorter acquisition time, and is more available and affordable than positron emission tomography, thus allowing access to cardiac imaging to a greater number of patients.

**Principles of CT**
The principle of CT involves the use of a thin fan beam of radiation passing through the body at different angles. After collimation of the beam to reduce scatter, the photons are recorded on a corresponding detector array, and the transmission data digitized into picture elements (“pixels”). A “filtered back projection” reconstruction algorithm, which takes into account the attenuation of the x-ray beam along its path, allows for reconstruction of the grayscale values of each pixel with reference to the value for water and air, to depict cross-sectional images.

The evolution of CT included consecutive steps with progressive improvement in spatial and temporal resolution. Conventional CT included the first through fourth generations of CT scanners. These progressed from involving both rotation and translation (first and second generations) to only rotation (third and fourth generations, also called dynamic CT) of the detectors and x-ray source, thereby decreasing scanning time and interscan delay. The parallel increase in the number of detectors and acquisition angle and the change from pencil to fan beam contributed to improved image quality and spatial resolution.

The new frontier of cardiac imaging, the Holy Grail of CT scanning, evolved rapidly over the 1980s and introduced some challenge because of the motion artifacts caused by cardiac contraction and respiratory motion. These limitations become particularly prominent at higher heart rates. Although scanning time of under half a second, coincident with the slow-filling phase of diastole, may provide adequate anatomic depiction of the heart, the rule of thumb for quantitative measurements of tissue opacity within a specific cardiac phase is the need for scanning time <100 ms per image (Figure 2). On the other hand, rapid scanning may degrade image quality, and the tradeoff between temporal and spatial resolution needs to be considered.

Indeed, the series of high-speed scanners introduced over the past 2 decades have shown varying degrees of temporal and spatial resolution (Figure 2) depending on the basic technology used to generate, move, and detect the x-ray beam.

**Fast CT**
In the late 1970s the first fast CT was proposed with specific indication for cardiac imaging. Since then, CT has under-
gone rapid technical changes; spatial resolution has especially increased, improving image quality. At present, the anatomy of coronary arteries (anomalies, visualization of bypass grafts, and detection of stenosis) and calcium scoring can be evaluated reasonably well, although plaque imaging and intracoronary stent visualization need further development. Furthermore, increased temporal resolution and improved spatial resolution paved the way to the dynamic evaluation of cardiac function.

**DSR**
The first 3D volume-scanning CT scanner with truly high temporal resolution was presented in 1980. The design of the dynamic spatial reconstructor (DSR) allowed rapid and repeated scanning of the heart (60 images per second) that reduced motion artifacts to depict dynamic changes in cardiac volume, capture the motion of the heart, and record contrast media distribution within the myocardium. This capability permitted, for the first time, accurate regional and global measurements and highlighted the important relationships between cardiac structure and function. However, the computing power that the DSR demanded was hard to meet at that time, and together with the relatively low signal:noise characteristics, resulted in discontinued use of this scanner.

**Electron Beam CT**
Electron beam CT (EBCT) was developed in 1984 and specifically designed for cardiac imaging. Because of the absence of any moving mechanical parts, its temporal resolution is 50 ms per set of 2 contiguous slices, with a repetition rate of 17 images per second. The technique has been successfully applied for quantification of coronary artery calcifications, noninvasive coronary angiography, ventricular anatomy, and global and regional function. Furthermore, it is among the few scanners capable of assessing myocardial perfusion (see below). However, the rapid scanning came at a cost of moderate image quality, further technical develop-
ment was rather restricted, and the availability of EBCT scanners remained limited.

Helical CT

Helical CT scanning, developed in the 1990s, has been placed at the center stage of clinical CT. This technique is based on simultaneous and continuous x-ray source rotation and patient translation. Modulation of the tube current and increased number of photons provide a high-quality 3D data set, an important improvement compared with EBCT that can afford only 2 current power settings.

Multidetector Helical CT

From the initial single slice per detector, helical CT has evolved to include a multirow detector array and the current 64-detectors CT,8 progressively increasing both the number of simultaneously acquired images and temporal resolution (Figure 2); 128- and 256-slice multidetector CT (MDCT) will probably be released before too long. Reconstruction algorithms and software capability have also been progressively improved. Unfortunately, because of the relatively long rotation time, their temporal resolution (165 to 400 ms per image) is still insufficient to permit a truly comprehensive assessment of cardiac function with MDCT and may necessitate the use of β-blockers to slow the heart rate.

Nonetheless, the remarkable ongoing evolution of fast CT scanners in terms of both speed and image quality continues to challenge investigators and clinicians to test their limits by designing and identifying novel applications for analysis of cardiac anatomy and function. Currently, these techniques are already able to assess functional parameters (Figure 1) related to the function of the cardiac pump (systolic and diastolic), wall (myocardial viability and motion), and tubing (vascular endothelial function, perfusion, and permeability).

Cardiac Applications of CT

Systolic Function

Left Ventricle

Guthaner et al9 were the first to demonstrate in 1985 the ability of EBCT for volume measurements. A year later the measurement of LV ejection fraction was validated by other research groups10,11 in animals and humans. Its accuracy for determination of ejection fraction was also validated against Tc-99m sestamibi first-pass angiography,12 radionuclide angiography, and cine angiography.13 Moreover, EBCT estimation of LV volumes (Figure 3) and mass agreed with 2D echocardiography. Indeed, Rumberger et al14 established EBCT as a recognized technique for evaluation of the heart because of its rapid image acquisition and reproducibility in patients with cardiac disease.15

In parallel, partly because of the cost and limited number of EBCT scanners that restricted access to this modality, the CT technology continued to evolve. Because of higher spatial resolution, the new-generation helical CT scanners delineate myocardial chamber contours and provide higher quality images compared with EBCT (Figure 4). Moreover, the ability to acquire consecutive thin slices and subsequently reformat them in different planes allows calculation of ventricular volumes in short axis reoriented images. Outlining chamber contours can be facilitated by semiautomatic thresholding techniques that decrease bias but may also introduce some error (eg, because of inadvertent inclusion of hematoma or thrombi).16

Moreover, the relatively lower temporal resolution of helical CT limits evaluation of the fast systolic phase, in particular at high heart rate (>65 bpm). It may miss the minimal LV systolic volume, which lasts for only 80 to 200 ms (of total systolic time of about 0.3 sec), potentially leading to overestimation of LV systolic volume and thereby underestimation of LV ejection fraction. Indeed, estimation of LV ejection fraction with 4-slice or 16-slice MDCT showed good correlation, although there was some underestimation compared with other techniques, like MRI and echocardiography.17–19

Measurements of end-systolic LV volume by 64-slice MDCT were also characterized by good correlation but some overestimation. Despite application of different volumetric modeling, such as 3D data set, geometric hemisphere cylinder, or geometric biplane ellipsoid methods, MDCT continued to show overestimation of end-systolic volume and, thus, mild underestimation of ejection fraction.20,21
Right Ventricle
The morphology of the right ventricle (RV) is more complex than that of the LV. In echocardiography, the RV may be difficult to visualize because of its retrosternal localization, and the current reference standard for estimation of RV function is 3D cardiac MRI. Because tomographic images obtained with x-ray CT are similarly unrestricted by geometric assumptions (Figure 3), CT is also suitable for RV measurements.

Accordingly, the global and regional function of RV has proved to be reliably assessed using EBCT under normal and pathological conditions. With the advent of the new generation of helical CT, the 16-slice MDCT was found to provide accurate and reliable noninvasive measurement of RV function. However, as for LV function evaluation, MDCT shows overestimation associated with underestimation of ejection fraction.

Diastolic Function
The techniques for routine clinical investigation of diastolic function are currently cardiac catheterization or echocardiography. EBCT can detect time dependent changes in LV volume throughout the cardiac cycle by scanning 8-mm–thick slices at ≤8 different levels of the heart (Figure 3). This allows quantitative analysis of regional and global diastolic function by calculating different parameters, such as peak-filling and peak-emptying rates, in each level or in the entire heart. EBCT evaluation of diastolic filling showed good correlation with radionuclide angiography and was subsequently used for physiological assessment in humans.

Myocardial Viability
Distinction among myocardial necrosis, hibernation, or stunning is fundamental for the prognosis and care of patients after myocardial infarction. MRI, contrast echocardiography, and single-photon emission CT are widely used for this purpose, but CT may also be a promising tool.

Evaluation of the status of the myocardial wall after infarction includes visualization of a hypoenhanced area in the early (3 to 6 sec after contrast injection) or late (7 to 10 minutes after injection) images and of a hyperenhanced area surrounding the dark area in late acquisitions. Both the single-slice and multislice CTs have been used to depict different patterns of reflow response and myocardial perfusion deficits. The CT techniques were compared with other methods, such as Tl201 single-photon emission CT, MRI, microsphere blood flow measurements, and postmortem myocardial staining in animal models and showed feasibility in humans as well.

Wall Thickness and Motion
Fast CT also allows evaluation of the global and regional ventricular geometry in relation to myocardial function. For example, EBCT successfully assessed variations in wall thickness and motion in both animals and humans at different cardiac levels. Similarly, the DSR was capable of evaluating the thickening and rate of motion of the cardiac wall.
The use of helical CT also provided noninvasive information of wall thickening and motion. Measurements of segmental wall motion by 16-slice MDCT showed good agreement with those obtained by echocardiography.

Microvascular Function

Evaluation of cardiac microvascular function using CT traces back to the classic indicator-dilution theory developed by Stewart–Hamilton, and the subsequent refinement and application of the method, which takes into account recirculation and assumptions regarding contrast medium kinetics. Displacement of a contrast medium bolus can be followed by repeatedly scanning cross-axial images of the heart at the same cardiac phase (usually during the least-motion end diastole); functional parameters can then be estimated from indicator-dilution curves externally detected during the bolus first pass (Figure 4). Mathematical models allow the estimation of physiological parameters, such as myocardial perfusion and microvascular permeability.

The DSR was initially used to demonstrate the feasibility of assessing regional myocardial blood supply, and at around the same time, Axel developed the basis for calculation of cerebral perfusion with CT, which was subsequently applied to the myocardium and other organs. In 1987, Rumberger et al. performed the first EBCT study on myocardial perfusion in a dog model and observed good agreement with simultaneously injected radiolabeled microspheres. Subsequent studies confirmed the feasibility of measurements of myocardial perfusion with EBCT over a wide range of perfusion rates and in humans, despite some underestimation of high flow rates compared with radiolabeled microspheres (Figure 4). Several approaches have been partially successful in overcoming this limitation, including correcting for the delay between the LV and myocardial peak opacification introduced by Gould et al. or for dynamic changes in myocardial vascular volume that parallel myocardial blood flow.

Subsequently, EBCT was successfully used for estimation of myocardial perfusion in various experimental models. EBCT detected the impaired increase in myocardial perfusion or blood volume in response to cardiac...
challenge in pigs with early atherosclerosis and discerned responses of different size microvessels to pharmacological intervention.\(^{47}\) Administration of endothelium-dependent and -independent vasodilators has shown its ability to detect early functional abnormalities of the myocardial microcirculation and evaluate the effect of acute or chronic drug treatment in improving these alterations.\(^{43,46}\) Furthermore, mathematical models applied to DSR\(^{49}\) or EBCT\(^{43–45,48}\) indicator-dilution curves allow estimation of myocardial microvascular permeability, an important index of endothelial function and integrity.

Moreover, specific mathematical modeling of the relationship between blood volume and perfusion also allowed characterization of the function of various sizes of intramyocardial vessels.\(^{50,51}\) Because the spatial resolution of whole-body CT (as opposed to micro-CT) is insufficient to visualize these microvessels (Figure 1), their function can be inferred using mathematical models and administration of size-specific vasodilators, which selectively affect specific vascular districts.\(^{46,47}\)

Although cardiac and myocardial microvascular function can be quite well characterized using the DSR and EBCT, the lower temporal resolution of MDCT is likely to diminish its capability for assessing flow but has yet to be fully determined. In a preliminary study, we compared myocardial indicator dilution curves obtained with EBCT and 64-slice MDCT in the same pig. As might be expected, we observed higher quality images with MDCT but noisier and less reproducible indicator-dilution curves (Figure 4). This could be related to the lower temporal resolution of MDCT compared with EBCT (165 versus 50 ms) but to other contributing factors as well, such as the location of the x-ray tube and angle of data acquisition, which are fixed with EBCT but may vary with MDCT at each cardiac cycle.

Nevertheless, the ongoing improvement in MDCT scanning and data acquisition protocols is promising. New faster devices with improved temporal resolution, like the dual-source CT,\(^{52}\) which may allow assessing myocardial microvascular function with MDCT without a need for heart rate control,\(^{53}\) may finally render MDCT an important diagnostic tool.

**Limitations**

In addition to technical issues mentioned earlier, the use of CT in clinical practice is associated with some additional limitations. The use of contrast media is restricted in some patients, particularly in those with iodine hypersensitivity or pre-existing renal disease. Notably, the dose of contrast media used for a functional CT study is less than that used during coronary angiography. Future technological advances are promising for further reduction in the administrated dose, and development of alternative contrast agents (eg, particulate) may decrease their risk. Nevertheless, the need for contrast media remains a clinical concern.

The radiation dose may vary depending on the scanning protocol. For example, the typical radiation dose absorbed during EBCT calcium scoring (0.5 to 0.7 mSv) increases to 0.8 to 1.5 mSv using 4- to 16-slice MDCT with prospective gating and to 6.2 mSv with retrospective gating.\(^{41}\) The new MDCT can decrease the radiation dose by exposure-control measures, such as ECG-controlled dose modulation, and adapting the current of mA to the body habitus of the patient.\(^{54}\) On the other hand, perfusion studies currently involve repeated scanning of the same myocardial region and, thus, are still associated with substantial radiation exposure, so that the cost–benefit should be weighed. Moreover, the new dual-source MDCT allows us to adapt the duration of x-ray tube current usage to heart rate,\(^{55}\) a feature that significantly reduces the radiation dose compared with the 16- and 64-slice MDCT.\(^{56}\)

Notably, the increasing girth of the patient population over the past decade requires boosting power (which, in turn, increases radiation exposure) and a wider bore to accommodate such patients (thereby limiting the speed of rotation and data acquisition), a trend that may pose a challenge for microvascular functional studies.

**Conclusions**

CT, thanks to its technical versatility, has marked potential for becoming central for the evaluation of cardiac and vascular function. However, since the early pioneering attempts to study the heart dynamically with DSR and, subsequently, EBCT, much of the development has focused on improving CT image quality rather than functional applications. This trend has paralleled the development of alternative useful modalities, such as positron emission tomography and single-photon emission CT, which are conceptually focused on functional and metabolic assessments.

For a decade, functional CT scanning of the beating heart has been available mainly using EBCT, which had been specifically designed for this purpose. However, its low availability and modest image quality have restricted cardiovascular use of CT to few centers. In recent years, however, significant development in CT technology and acquisition protocols succeeded in improving both speed and image quality, opening new horizons for clinically useful dynamic studies of the cardiovascular system. Additional developments in computing power for complex data handling and display, and rapidly decreasing costs of data archiving and compression, may make this strategy feasible.

Therefore, CT scanning may become a routine technique for the evaluation of patients with or at risk for cardiovascular disease. Indeed, CT embodies many characteristics that favor its use for the diagnosis, treatment, and follow-up of cardiovascular disease.

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**References**


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