Coronary CT: drug-induced stress examination technique for studying coronary arteries

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Abstract

Coronary CT is a low-invasive diagnostic examination that uses contrast medium to explore the coronary arteries, the cardiac cavity and assess the condition of the vessel walls.
It is an examination with greater accuracy than other diagnostic and clinical investigations; in fact, it allows the detailed acquisition of ultra-thin anatomical sections of the coronary vessels and their reconstruction in every plane of space.
Intravenous injection of the contrast medium bolus and cardio-synchronisation enable non-invasive angiography of the coronary arteries, with high anatomical detail and excellent diagnostic accuracy very close to invasive coronarography.
However, this method is not to be considered as an alternative to coronarography, but rather as a complementary diagnostic aid; in fact, the invasive technique remains the approach of choice in patients with acute coronary syndromes. Coronary CT is prescribed in cases of: suspected coronary artery obstruction or stenosis, high risk of atherosclerosis and coronary artery disease, heart failure, dilated cardiomyopathy, patients undergoing cardiac and vascular surgery, such as aortic aneurysms, patients who are candidates for minimally invasive percutaneous aortic valve replacement (TAVI).
The examination can be performed during a resting phase or during a phase in which the patient is under drug-induced stress; in particular, coronary-CT under stress represents a further step forward for this method.
The execution of the examination protocol under pharmacological stress leads to greater diagnostic accuracy, since by combining the information provided by anatomy and perfusion it allows both morphology and cardiac function to be assessed.
The assessment of myocardial perfusion is based on the distribution of iodinated contrast during its passage through the myocardium; since the distribution of contrast medium is determined by the arterial blood supply, myocardial perfusion defects can be identified as hypo-attenuated areas containing reduced amounts of contrast.
A perfusion defect under pharmacological stress that reverses at rest is, by definition, a stress-induced ischaemia, in contrast, an irreversible defect is characteristic of myocardial infarction.

Introduction

Technological developments in recent years have enabled significant innovations to be made to traditional diagnostic procedures, particularly in the field of computed tomography, which has made it possible to include coronary CT among the primary methods in the diagnostic pathway of coronary artery disease.
Coronary CT is a low-invasive diagnostic examination that allows exploration of the coronary arteries, the cardiac cavity and an assessment of the state of the vessel walls. Intravenous injection of the contrast medium bolus and cardio-synchronisation enable non-invasive angiography of the coronary arteries, with high anatomical detail and excellent diagnostic accuracy very close to invasive coronarography [1].
Pharmacologically induced stress, following the resting phase, has the potential to assess a broad spectrum of coronary vascular dysfunction and ventricular perfusion problems.
However, this method is not to be considered as an alternative to coronarography, but rather as a complementary diagnostic aid; in fact, the invasive technique remains the approach of choice in patients with acute coronary syndromes [2].
This paper bears the burden of illustrating this method, highlighting its advantages in a twofold perspective: exposing its aspects from a purely technical point of view, but reminding the technician to keep the humanity ingenuous in his gaze, being yes, able to be impeccable in his work, but at the same time to be a shoulder, if necessary, for those in front of him.

Stress-inducing drugs:

CT examination of the coronary arteries directed towards the evaluation of myocardial perfusion involves the administration of pharmacological agents capable of inducing vasodilation; the administration of these drugs is necessary in order to induce the patient under conditions of pharmacological stress suitable for demonstrating the presence of perfusion deficits, i.e. inducible ischaemia.
For this purpose, various vasodilating agents such as adenosine, regadenoson, nitroglycerine and β-blockers can be used; the one most commonly used in Europe is adenosine: safe, relatively inexpensive, effective and with a very short half-life of 2-10 s; in Asian countries it is preferred to be replaced by

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adenosine triphosphate (ATP) due to its lower cost. It is essential that patients have not consumed caffeine in the 24 hours prior to the adenosine infusion, as this can interfere with its metabolism [3]. Other drugs used include regadenoson, a more potent vasodilator than adenosine that shows selectivity for the coronary circulation rather than the renal, peripheral and mesenteric circulation; unlike adenosine it does not cause negative chronotropic (reduction in heart rate), negative dromotropic (slowing of the conduction velocity of the heart's electrical impulse at the level of the atrial and ventricular musculature) and negative inotropic (reduction in contraction force) effects [4].

The main advantage of regadenoson is that it can be used in patients with asthma and chronic obstructive pulmonary disease; on the other hand, the main disadvantages include higher costs and a longer half-life. The administration of sublingual nitroglycerin improves the accuracy of the examination, as influencing the epicardial coronary arteries by vasodilation improves the visualisation of possible stenosis, but can also reduce hypoperfusion in some cases. Sublingual nitro-derivatives are generally used in conjunction with β-blockers, i.e., drugs that reduce heart rate and blood pressure; although there are conflicting data on their use, as they may lead to the masking of ischaemia, (so much so that some suggest their strict contraindication in other perfusion techniques such as SPECT), there are no data to suggest that these problems may occur in perfusion CT studies [5].

Furthermore, intravenous administration of short half-life β-blockers may be an alternative to avoid the aforementioned masking.

***Protocol at rest and under stress*:**

After obtaining the justification for the examination and completing the informed consent form and pregnancy form in the case of female patients of childbearing age, the patient is asked to uncover the chest and remove all metal objects present (bra, necklaces, corsets, etc.). This is followed by verification of the parameters necessary for the investigation, including blood tests and biometric parameters (heart rate, blood pressure, weight and height).

The patient is positioned supine on the couch with arms in abduction with subsequent placement of the electrodes for ECG monitoring and cardio-synchronisation (Fig. 1).

The heart must be at the isocenter of rotation of the tube-detector system, taking the left paramedian line and the anterior axillary line in the lateral for centering. In the case of right-cardia, the reference line will be the right paramedian line. Once the patient is positioned, the automatic injector will be connected to the previously positioned peripheral venous access for the administration of the contrast medium [6].

After the acquisition of a topogram (scout-view) in antero-posterior and lateral views, a scan without contrast medium is taken, extending from the jugular to approximately 5-6 cm below the xiphoid process of the sternum.

This preliminary acquisition is useful both in order to define the cranial and caudal limits of the subsequent angio-CT acquisition and for the evaluation of atheromasic plaques present in the coronary arteries; in fact, by means of the 'calcium score', i.e. dedicated processing software, it is possible to assess the possible presence of atheromasic plaques. The calcium score is a quantitative analysis that makes it possible to establish the risk of an ischaemic cardiovascular episode based on the amount of calcium accumulated in the coronary vessel wall.

The contrastographic study of the coronary arteries can be performed in static or dynamic mode. Acquisition in static mode involves a single temporal phase during the first arterial passage of the contrast agent; dynamic acquisition, on the other hand, allows the acquisition of several consecutive phases during the transit of the contrast bolus through the myocardium. This modality, by calculating a time-attenuation curve (CAT), allows myocardial perfusion parameters such as blood flow (MBF) and blood volume (MBV) to be obtained. Acquisitions may follow a combined rest/stress or stress/rest protocol; both phases are necessary to accurately discriminate ischaemic and necrotic myocardium. Typically, the assessment of static perfusion at rest is derived from the anatomical acquisition of the coronary arteries; otherwise, dynamic perfusion acquisition can be performed in both stress and resting states for quantitative measurements of coronary flow reserve [7].

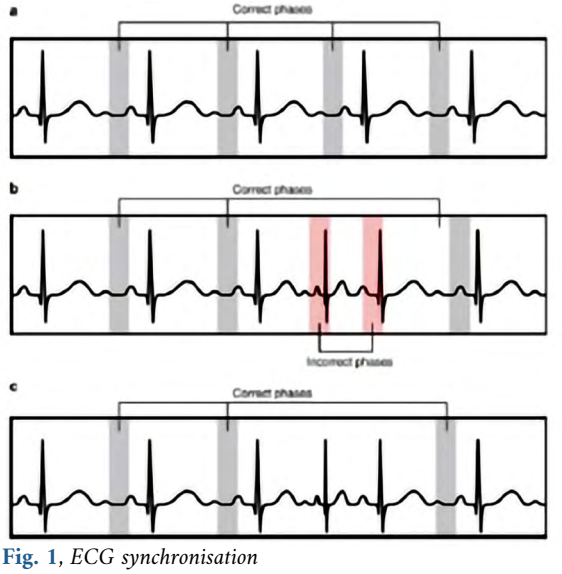

Fig. 1, *ECG synchronisation*

The state of stress is induced by administering vasodilator drugs (adenosine, regadenoson, nitroglycerine, β-blockers) suitable for demonstrating the presence of perfusion deficits.

For the angiographic phase, the most commonly used method in cardio-CT is automatic bolus triggering, in which the opacification trend of a ROI (Region

ESSAY
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Of Interest) is monitored over time and, when this opacification reaches the threshold HU value (usually 200 HU with a high concentration contrast agent) the system starts with the minimum post-threshold delay set by the operator (time between reaching the threshold value and the start of the angiographic acquisition) with inspiratory instructions. The region of interest is usually positioned within the ascending aorta and the scan is performed cranio-caudally in inspiratory apnea.

The criterion for the correct execution of the angiographic phase of this examination is the maximum opacification of the left portion of the heart, with consequent filling of the coronary arteries. The right portion of the heart, on the other hand, must be completely free from the presence of contrast medium, which must extend from the pulmonary arterial trunk to the left ventricular apex.

The anatomical volume to be examined is considered on the basis of the clinical question; in fact, for the study of the coronary circulation it is sufficient to limit the acquisition from the tracheal bifurcation to the diaphragm, in the case of the evaluation of coronary bypasses, on the other hand, it is necessary to extend the field of acquisition up to the aortic arch.

Two different acquisition techniques can be chosen to perform this examination: the retrospective gating technique, which is based on a volumetric spiral scan, and the prospective gating technique, which is based on a sequential axial scan.

These approaches differ in terms of acquisition, but also differ in terms of scanning parameters; they tend to work with 80-120 Kv with automatic milliampere modulation, based on a reference index: in the case of lean patients the mA will be reduced, while for robust patients it will be increased, with the aim in both cases of maintaining a certain image quality.

In general, this examination is distinguished from other contrastography studies by the use of a low pitch value and thus by the lower movement speed of the couch and the maximum rotation speed of the X-ray tube, the aim being to achieve high spatial resolution, high temporal resolution and at the same time low exposure.

Late Enhancement:

Following the acquisition of the cardiac arterial phase, an additional late enhancement study can be performed to assess any disparity in iodine concentrations between scarred and unscarred regions, observed through areas of late iodine enhancement.

This study consists of an additional administration of contrast medium about 10 minutes after the stress-rest study; it is recommended to achieve a dose of contrast medium equivalent to a total body examination in order to obtain sufficient differentiation between healthy and pathological myocardium.

The acquisition is performed with a prospective triggering technique synchronized to 75% of the cardiac cycle phase, with scanning parameters adjusted according to the patient's body mass index.

Generally, a late enhancement scan is performed using reduced tube voltage and/or tube current, both for dosimetric reasons and to improve differences in iodine contrast concentration between scarred and unscarred myocardium. Although a reduction in tube voltage helps to improve image contrast simultaneously, it leads to an increase in image noise. The acquisition protocol may vary depending on the specific clinical practice or study conducted, as well as the availability or non-availability of Dual Energy technology.

The introduction of dual-energy CT (DECT) has alleviated some of these technical limitations; in fact, studies using dual-energy technology have produced the most favorable results. Any abnormalities caused by heart wall motion can be assessed through Cine images to further improve the sensitivity and specificity of the late study; subsequently, Cine-TC images can be reconstructed in short-axis and long-axis, and along four-chamber and three-chamber planes [8].

An element of great diagnostic utility is the extracellular volume fraction (ECV), i.e. the volume of tissue that is not occupied by cells; it is calculated on cine images using a method derived from image subtraction: regions of interest (ROI) are drawn on the left ventricular myocardium and the blood pool; from these, attenuation values are extracted. before and after contrast medium injection; finally, these values are corrected by reference to haematocrit values.

ECV is a marker of myocardial tissue remodeling and provides a physiological unit of measurement: ECV values are considered increased when they are 27% or higher, and ECV values widely above 45% are suggestive of cardiac amyloidosis; low ECV values occur in thrombus and lipomatous metaplasia. Besides amyloid, an increased ECV is often due to excessive collagen deposition and is thus a more robust measure of myocardial fibrosis.

Through this type of study, a possible myocardial scar is defined as a focal area of increased attenuation relative to the surrounding myocardium; it may be ischaemic or non-ischemic and can be assessed in its transmural extent, and segmental cardiac involvement with similar accuracy to MRI.

Post-processing:

Post-processing is the final part of the CT examination that supports and precedes the processing of the report. Once the raw data set is available, one only knows the sum of the attenuation values, but one does not know their spatial position.

The back-projection algorithm allows the image, albeit raw, to be formed. Kernel convolution filters that harmonise the resolution of adjacent pixels are required to approximate the concept of a diagnostic image. The choice of convolution kernel is influen-

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ced by the amount of noise and the resolution of the raw images.
Applying a convolution kernel to the sinogram data and then applying the back projection algorithm is the mechanism of the most common image reconstruction method: Filtered Back Projection (FBP). FBP produces noisy images when working at a low dose, which is why iterative reconstruction algorithms were developed. Operational reconstructions are basically divided into:
statistical reconstruction methods that perform an iterative loop in the image domain only;
hybrid statistical reconstruction algorithms that work in both image space and raw data;
iterative algorithms that work only on the raw data also known as model-based iterative reconstructions.
The raw data obtained are subjected, via dedicated software, to post-processing algorithms whose aim is to generate reconstructions that improve the accuracy and diagnostic quality of the images together with quantitative values on the degree of stenosis, cardiac function and the presence of calcium in the coronary arteries, i.e:

- Multiplanar Reformation (MPR);
- Maximum Intensity Projection (MIP);
- Volume Rendering (VR, Fig. 3-4).

Multiplanar reconstruction (Fig. 2) is a type of algorithm that makes it possible to create a two-dimensional image, oriented along an arbitrary plane, from a dataset of coplanar images. In detail, information on the position and density (expressed as a greyscale brightness value) of voxels belonging to images acquired in parallel planes (e.g. a series of axial images) is used to generate an image whose voxels are geometrically projected onto an operator-defined plane with a different inclination (coronal, sagittal or oblique), depending on the position and density value of the voxels belonging to the native images.
In this way it is also possible to simultaneously compare MPR images in the three standard planes, allowing for a multiplanar view; to be able to achieve this, the native image dataset must consist of isotropic voxels, a condition that has now been made possible thanks to modern multi-layer CT machines.
Typical application of this algorithm is in the study of vessels; a variant of this algorithm is the curvilinear reconstruction (CPR, Curved Planar Reformation, Fig. 5), which makes it possible to reconstruct the course of the coronary arteries, in a single plane, by generating longitudinal cross-sections of them.
Advanced third-generation iterative algorithms are used to reconstruct the data with different convolution filters Bv (Body vascular).

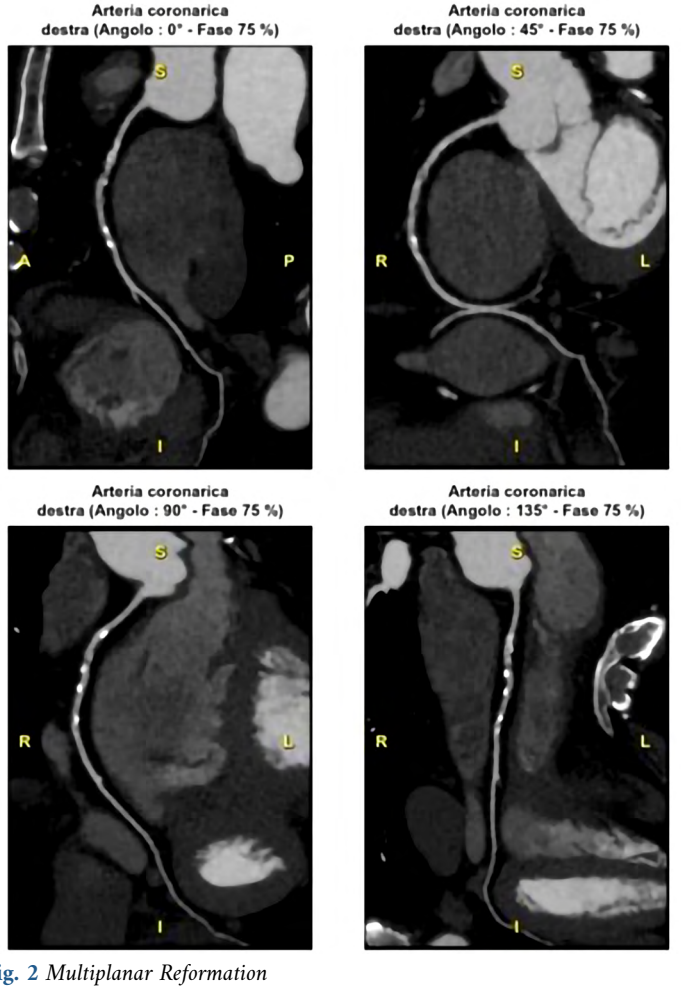

Fig. 2 *Multiplanar Reformation*

ESSAY
JAHC | JOURNAL OF ADVANCED HEALTH CARE
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For example, filters Bv36, Bv40, Bv44 and Bv49 are used. It should be noted that the higher the Bv filter number, the harder the image will be.

With the maximum intensity projection algorithm, a volume with an operator-defined thickness and orientation is selected and only voxels with higher intensities (i.e. higher density) are represented in the reconstructed image. As a consequence, the MIP image makes it possible to show anatomical structures with homogeneous intensities that are not included in their entirety within a single axial scanning plane, such as coronary arteries, by following the course of several vessels at the same time and thus obtaining angiographic-like reconstructions of the entire coronary tree.

The volume rendering algorithm makes it possible to obtain three-dimensional images of the anatomical structures under examination, which are more easily assimilated to the real anatomy of the patient (Fig. 3-4).

The spatial and contrast information contained within the 'raw data' is used in its entirety and the resulting image represents an average of the intensity of all voxels contained within that volume; each voxel is assigned an opacity, transparency and colour value depending on its intensity, position and projection from which the volume is observed (Fig. 6-7).

Such an algorithm is used in special cases such as coronary fistulas or the presence of abnormalities that need to be better visualised for purely aesthetic reasons as these are not diagnostic images.

Post-processing makes it possible to improve or eliminate any artefacts present in the images. The most common artefacts that need correction are: motion artefacts due to elevated heart rate or respiration, spatial misalignment artefacts and beam hardening artefacts that can also mimic perfusion defects, causing diagnostic errors.

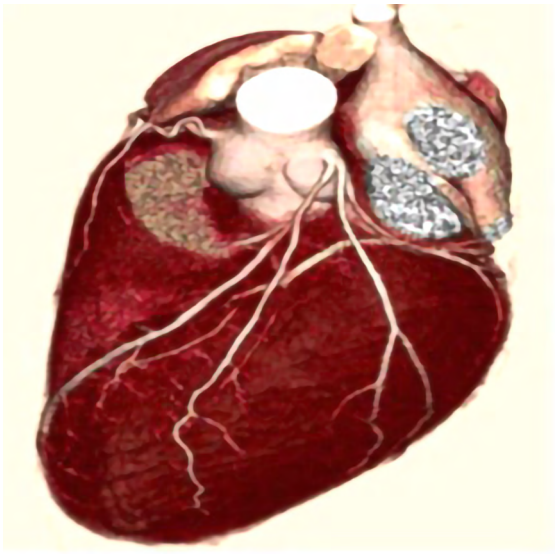

Fig.3 *Riconstruction VR*

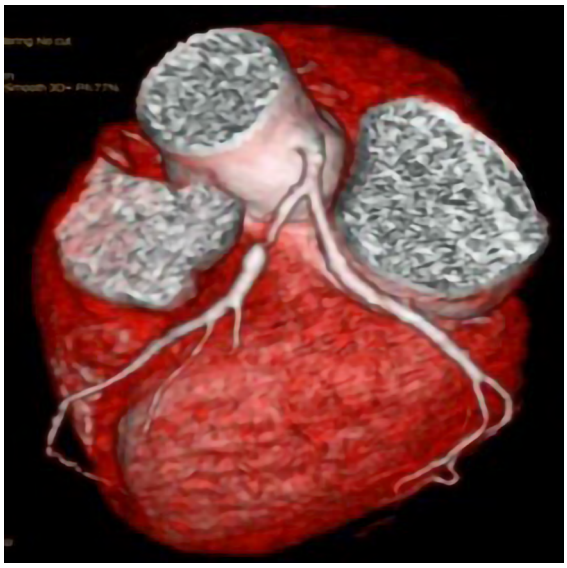

Fig.4 *Vessel stenosis and ectasia in VR*

Fig. 5, *Reconstruction CPR*

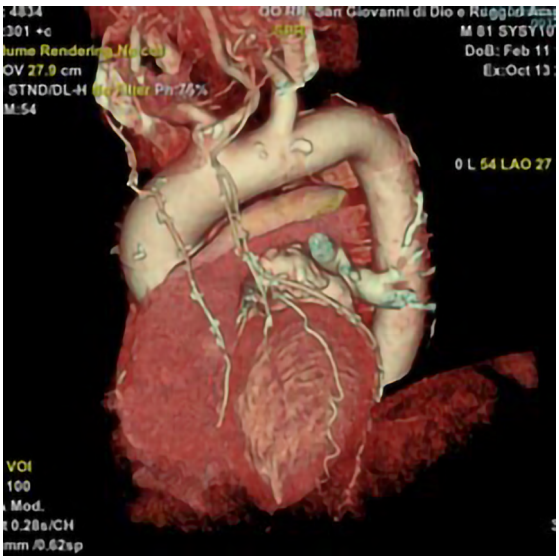

Fig. 6. *VR Reconstruction of myocardium*

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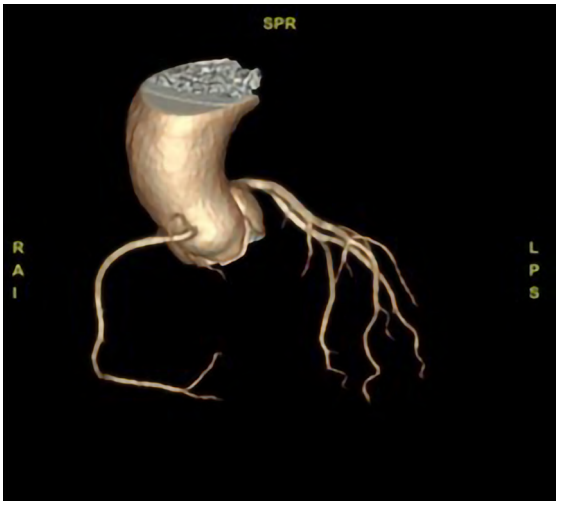

Fig. 7. *VR Reconstruction of vessels*

Conclusions

Performing the examination protocol under pharmacological stress leads to greater diagnostic accuracy, as by combining the information provided by anatomy and perfusion it allows both morphology and cardiac function to be assessed.

Prior to the acquisition, an intravenous infusion of a vasodilator such as adenosine is performed, so as to induce pharmacological stress conditions in the patient that are suitable for demonstrating the presence of perfusion deficits, i.e. inducible ischaemia; consequently, the administration of this drug results in a significant optimisation of the quality of the diagnostic procedure [9,10].

The assessment of myocardial perfusion is based on the distribution of iodinated contrast during its passage through the myocardium; since the distribution of contrast medium is determined by the arterial blood supply, myocardial perfusion defects can be identified as hypo-attenuated areas containing reduced amounts of contrast.

A perfusion defect under pharmacological stress that reverses at rest is, by definition, stress-induced ischaemia, in contrast, an irreversible defect is characteristic of myocardial infarction [10-13].

There are several debates in the literature on protocols with their advantages and disadvantages, e.g. the stress/rest protocol, which is more sensitive in detecting ischaemia, should preferably be used in patients with a high pre-test probability of coronary artery disease or when it is already known.

On the contrary, the rest/stress protocol should be the first choice in patients with a low to intermediate pre-test probability: when no or minimal coronary artery disease is detected during the rest phase, it is stopped, reserving pharmacological stress for patients with moderate to severe risk.

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