Adenosine-stress dual-source CT dynamic myocardial volume perfusion imaging: Initial clinical experience

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Purpose

Morphological evaluation of the coronary arteries has been shown to be insufficient for the comprehensive evaluation and management of individuals with suspected coronary artery disease (1, 2). In clinical practice the physiological significance of coronary artery stenosis is ordinarily assessed with myocardial perfusion imaging modalities during pharmacologically induced hyperemia. Single photon emission computed tomography (SPECT) (3) is the most widely used modality, although cardiac MRI (4) has demonstrated its superiority for detecting non-transmural perfusion defects mainly due to its higher spatial resolution (5).

The usefulness of multi detector-row CT (MDCT) for ruling out significant coronary artery stenosis (6-8) and for providing prognostic information in patients with suspected coronary artery disease (9-12) has repeatedly been demonstrated. Moreover, recent literature suggests the feasibility of using MDCT as a standalone technology for integrative evaluation of coronary heart disease (13-17). The standard spiral acquisition mode of MDCT, however, cannot dynamically evaluate the time-resolved passage of contrast medium through the myocardium and thus provides only limited information on the severity of microvascular obstruction.

The greater detector coverage of second generation dual-source CT (DSCT) (18, 19) may enable the performance of dynamic myocardial volume perfusion imaging of the heart by means of a dedicated "shuttle" mode, comprising rapid ECG-triggered image acquisition at two alternating table positions during contrast medium infusion.

This investigation aimed at determining the feasibility of applying this technique for the qualitative and (semi) quantitative CT assessment of myocardial perfusion during adenosine stress using stress/rest perfusion and delayed enhancement MRI as the reference standard.
Adenosine-stress dual-source CT dynamic myocardial volume perfusion imaging:
Initial clinical experience

Gorka Bastarrika1,2, MD, PhD; Luis Ramos-Duran1, MD; Michael A. Rosenblum3, MD; Doo Kyoung Kang1,4, MD; Garrett W. Rowe5, BS; U. Joseph Schoepflü,6,3, MD

1Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC
2Department of Radiology, University of Navarra, Pamplona, Spain
3Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, SC
4Department of Radiology, Ajou University Hospital, Suwon, South Korea

Fig. 0

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Methods and Materials

The study protocol was approved by our institutional review board and all patients gave written informed consent. Ten consecutive symptomatic subjects with known or high likelihood of coronary artery disease prospectively underwent stress/rest perfusion and delayed enhancement MRI and stress-perfusion and delayed enhancement cardiac CT. Subjects with known contrast media allergy, impaired renal function (creatinine >1.5 mg/dl), severe arrhythmia (e.g. atrial fibrillation), claustrophobia, or MRI-incompatible implanted devices were excluded from participation. All subjects underwent both procedures within 24 h.

Cardiac MRI acquisition protocol

MRI studies were performed using a 1.5-T system (Magnetom Avanto, Siemens, Erlangen, Germany) using a 6-element phased array coil. Stress perfusion MRI was performed three minutes into the intravenous infusion of adenosine (140 mg/kg/min Adenoscan, Astellas, Tokyo, Japan) using steady-state free precession (SSFP, TrueFISP Siemens) perfusion sequences. Three short axis sections representative of basal, mid, and apical myocardial portions were acquired with the following parameters: repetition time (TR) 2.8 ms, echo time (TE) 1.21 ms, flip angle 50°, inversion time 120 ms, field of view 380×80.2 mm, matrix 116x192, acquisition duration 150 ms, slice thickness 10 mm, 50 measurements, and an acceleration factor of 2 (GRAPPA, Siemens). Ten minutes after stress perfusion, rest perfusion images were obtained in the same technique. Contrast enhancement during stress and rest perfusion MRI was accomplished with gadopentetate dimeglumine (Magnevist, Bayer-Schering, Berlin, Germany; 0.05 mmol/kg each for rest and stress MRI perfusion imaging, 0.1 mmol/kg total), injected at 4 ml/s followed by 15 ml of normal saline. In addition, functional analysis was performed with retrospectively ECG-gated 8 mm slice-thickness cine loops in short and long axis views using a SSFP sequence (TR: 3.09 ms, TE: 1.3 ms, flip angle 80°, field of view 280×375 mm, matrix 156x192, twenty-five phases per cardiac cycle, no interslice gap, in-plane resolution 1.7×1.7 mm). Finally, delayed images were acquired using a phase sensitive inversion-recovery (PSIR) gradient echo SSFP sequence (TR: 3.38 ms, TE: 1.4 ms, flip angle 45°, field of view: 340×68.8 mm, matrix 127×256, slice thickness 8 mm, no interslice gap).

Cardiac CT acquisition protocol

All patients underwent cardiac CT using a second generation dual-source CT system (SOMATOM Definition Flash, Siemens). Initially, single heart-beat CT calcium scoring was acquired with the following parameters: 2×64×0.6 mm detector collimation resulting
in 2×128×0.6 mm sections by means of the z-flying focal spot technique, 280 ms gantry rotation time, 120 kV tube potential and 73mA per rotation tube current time product. Subsequently prospectively ECG-triggered coronary CT angiography was performed. Contrast medium enhancement was achieved using a triphasic injection protocol with injection of 70 ml of pure, undiluted iodinated contrast material (iopromide, Ultravist 370 mgI/ml, Bayer-Schering) followed by a constant volume of 50 ml of a 70%:30% saline-to-contrast medium mixture and 30 ml of pure saline, all injected at 6 ml/s through an 18G intravenous antecubital catheter using a dual-syringe injector (Stellant D, Medrad, Indianola, PA, USA). The study acquisition delay time was estimated by injection of a 15 ml contrast medium test bolus at 6 ml/s, followed by 50 ml of saline. The actual delay time was calculated as the time of peak contrast medium attenuation in a region of interest in the ascending aorta plus four seconds. For prospectively ECG-triggered coronary CT angiography, acquisition parameters were 2×64×0.6 mm detector collimation resulting in 2×128×0.6 mm sections, 280 ms gantry rotation time, and 320mAs per rotation tube current time product. 120kV tube potential was used, since all ten patients had a body mass index of >25 kg/m². Acquisition was cranio-caudal from above the origin of the coronary arteries to below the dome of the diaphragm. Adaptive prospective ECG-triggering was used with the full radiation dose window set at 70% of the R-R’ interval in patients with heart rates #70 beats per minute (bpm), and 40% of the R-R’ interval in patients with a heart rate of >70 bpm. Reduced dose (20% of the nominal tube current) was applied between 30% and 90% of the R-R’ interval to obtain functional information during these cardiac phases. For coronary artery evaluation datasets were reconstructed using 0.75 mm section thickness and 0.3 mm reconstruction increment at 40% or 70% R-R’ depending on the heart rate. An additional reconstruction was performed during systole at 250 ms after the R-peak to plan the coverage range for the myocardial perfusion acquisition.

Myocardial perfusion imaging was performed using a dynamic acquisition mode three minutes into adenosine (140 mg/kg/min) stress. Data were acquired at two alternating table positions in ECG-triggered mode during end systole (250 ms after the R-peak), with the table shuttling back and forth between the two positions (table acceleration: 300 mm/s²) during image acquisition. Given a detector width of 38 mm, and a 10% overlap between both acquisition ranges, the anatomic coverage of this imaging technique is 73 mm. Image acquisition parameters were 100 kV tube voltage and 300 mAs. The image acquisition sequence was initiated four seconds prior to the arrival of the contrast medium bolus front as determined by the initial test bolus injection in order to ensure baseline acquisition of non-contrast images prior to the onset of first-pass perfusion. Myocardial perfusion studies were contrast medium enhanced with 50 ml of iopromide, followed by 50 ml of saline, injected at 6 ml/s. Including test bolus acquisition and coronary CTA angiography, each patient thus received a total volume of 150 ml contrast medium and 135 ml saline. Studies were obtained during end-inspiration with a standardized acquisition time of 30 seconds. If patients could not hold their breath for 30 seconds, they were instructed to slowly release their breath and continue breathing shallowly.
Images were reconstructed with 3 mm slice width every 2 mm with a medium sharpness convolution algorithm and then processed using the Volume Perfusion software (syngo VA31, Siemens).

Finally, delayed enhancement studies were performed six minutes after perfusion imaging using a regular prospectively ECG-triggered mode with image acquisition at 70% of the R-R’ interval at 80 kV and 320 mAs. For delayed enhancement imaging, no functional image information was acquired.

**Perfusion data analysis**

Two experienced radiologists independently evaluated MRI and CT studies blinded to clinical history. Discordant findings were reconciled during a consensus read.

For qualitative analysis dynamic stress CT perfusion and MRI studies were interpreted visually in conjunction with delayed enhancement CT and MRI viability scans. On both, CT and MRI, a myocardial segment was considered as showing reversible ischemia when hypoperfusion lasted for more than six heart beats under adenosine stress without delayed enhancement on viability scans. Myocardial perfusion defects were classified as fixed if the hypoattenuation lasted for more than six heart beats under adenosine stress and delayed enhancement was seen on viability scans. Homogeneously perfused myocardium during adenosine stress that did not show delayed enhancement on viability studies was classified as normal (20).

Semi quantitative perfusion analysis was performed on 10 mm slice thickness short-axis multiplanar reformats of the stress cardiac CT acquisitions, representative of basal, mid, and apical portions of the left ventricular myocardium as well as on the three short-axis sections acquired at stress perfusion MRI. A commercially available software application (Argus, Siemens) was used for this purpose for both, CT and MRI studies. CT and MRI studies were evaluated in random order using the 16-segment American Heart Association model (21). The segments were automatically traced by the software after epicardial and endocardial borders were manually defined. Semi quantitative perfusion analysis was based on computing the upslope of the signal intensity over time curve from unenhanced myocardium to maximum signal intensity during the myocardial first pass of the contrast agent, according to the "myocardial-to-left ventricular upslope index" method (22). All parameters were normalized to blood pool signal intensity curves (22, 23).

Absolute myocardial perfusion quantification was performed based on dynamic perfusion CT studies using a prototype version of the Volume Perfusion software (syngo VA31, Siemens). A dedicated parametric deconvolution technique based on a two compartment model of intra- and extravascular space was used to fit the time attenuation curves. For increasing the precision of the fit, double sampling of the arterial input function (AIF)
was performed. The input function was sampled in the descending aorta at every table position and combined into one AIF that had twice the sampling rate of the tissue time-attenuation-curve (TAC). The algorithm then determined the maximum slope from the fit model curve for every voxel and calculated myocardial blood flow (MBF) according to the following relationship: MBF = Max Slope (TissueTAC) / Maximum (AIF), where the maximum slope reflects the tissue time-attenuation-curve and the maximum (AIF) indicates the maximum AIF value.

Statistical analysis

Data are expressed as mean ± SD. Interobserver agreement for visual assessment of myocardial perfusion defects was calculated with Cohen kappa statistics (24), and interpreted as follows: less than 0.20, slight or poor agreement; 0.20-0.40, fair agreement; 0.41-0.80, moderate agreement; greater than 0.80, excellent agreement. Qualitative estimation of perfusion CT and MRI were compared on a per-segment basis to determine sensitivity, specificity, positive and negative predictive values for the detection of myocardial perfusion defects. Dynamic first-pass perfusion results were evaluated using paired Student’s t-test or Wilcoxon signed-rank test, where appropriate. Bland-Altman analysis was performed to determine agreement between the upslopes of myocardial signal intensity curves estimated by CT and MRI. Spearman’s coefficient of rank correlation (rho) was calculated to assess correlation between dynamic perfusion CT-derived myocardial signal intensity upslope and MBF and interpreted as follows: 0-0.1: very low, 0.11-0.30: low, 0.31-0.5: moderate, 0.51-0.7: high, 0.71-0.9: very high, 0.91-1: almost perfect. A p level < 0.05 indicated a statistically significant difference. Data analysis was performed with commercially available statistical software packages (WINPEPI, version 8.8, PEPI-for-Windows; MedCalc, Version 9.3.0.0. MedCalc Software; Mariakerke, Belgium, and SPSS for Windows, version 15.0, SPSS Inc., Chicago, IL, USA).
Fig. 0

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Results

Clinical characteristics of the patient population

All study procedures were successfully completed in all subjects, without any adverse events. Demographic characteristics of the study population are shown in Figure 1. The mean age of the 10 subjects (8 male, 2 female) included in the study was 62.7±7.1 years (range: 51-71 years). Subjects’ mean heart rates during rest and under adenosine-induced stress did not significantly differ between CT and MRI exams. Mean total dose length product (DLP) of the four components (calcium scoring, coronary CT angiography, perfusion, delayed enhancement) of the cardiac CT protocol was 1290.4±233.3 mGy cm (range: 935-1776 mGy cm). The dynamic CT perfusion study by itself resulted in a mean DLP of 733.5±139.6 mGy cm (range: 508-971 mGy cm).

Coronary CT angiography

Evaluation of coronary CT angiograms ruled out significant coronary artery stenosis in four patients (Figure 2). Coronary CT angiograms showed occlusion of the distal right coronary artery (RCA) in one patient (Figure 3), significant stenosis of the proximal circumflex artery (Cx) in another patient, and significant stenosis of the distal RCA in a third patient (Figure 4). In the two subjects with prior bypass surgery, one showed occlusion of a left internal mammary artery to left anterior descending coronary artery (LAD) graft and the second patient had occlusion of the LAD distal to the left internal mammary artery graft anastomosis. In the two patients with prior stent placement (one of them also had a bypass), all stents (n = 3) were patent on coronary CT angiography.

Qualitative assessment of myocardial perfusion

Seven segments in 4 patients were excluded from analysis due to limited anatomic coverage of the dynamic CT perfusion acquisition mode (segment 1 in three patients, segment 6 in two patients, and segments 7 and 12 in one patient). Artifacts on one stress MRI study prohibited adequate assessment of the apical segments of the left ventricle in one patient (segments 13-16). Therefore, a total of 149 segments (93.1%) were included for analysis.

Interobserver agreement for detecting myocardial perfusion defects on CT and MRI was excellent (κ = 0.85 and κ=0.86, respectively). Visual assessment of MRI perfusion studies showed perfusion defects in 36 myocardial segments (39.1%) in six patients. Twenty nine of these perfusion defects were fixed whereas seven represented reversible ischemia. Dynamic stress CT perfusion correctly classified 31 of these perfusion defects
but missed five (two reversible) detected on MRI. Overall, dynamic perfusion CT had 86.11% (71.34-93.92%) sensitivity, 98.23% (93.78%-99.51%) specificity, 93.9% (81.79-98.17%) positive predictive value, and 95.7% (91.03-97.98%) negative predictive value in comparison with perfusion MRI for detecting any type of myocardial perfusion defect on a segmental basis.

**Semiquantitative assessment of myocardial perfusion**

At dynamic stress perfusion CT, estimation of the upslope of the signal intensity over time curve between normal (5.4±2.1 SI/s) and hypoperfused (4.4±1.5 SI/s) myocardium showed significant differences (p = 0.01). These differences were also significant in stress MRI studies (5.1±2.2 SI/s and 3.8±2 SI/s, respectively, p < 0.01) (Figure 5). Overall, when dynamic stress perfusion CT and semi quantitative stress perfusion MRI data were compared, no statistically significant difference was observed for the upslope of the signal intensity over time curve (4.8±2.3 SI/s for MRI and 5.2±2 SI/s for CT) (Figure 6), with dynamic CT mildly overestimating the upslope (mean difference of 0.3 SI/s, 95% confidence limits of agreement: -0.03 to 0.71) (Figure 7). Comparison of this parameter showed similar results when normal and hypo-perfused myocardial segments were compared separately.

**Quantitative assessment of CT myocardial perfusion**

Mean MBF of all myocardial segments at dynamic stress perfusion CT was 115.9±46.5 ml/100 ml/min (range 43.1-277.8 ml/100 ml/min). There was a significant difference in MBF values between normal (122.2±49.4 ml/100 ml/min) and hypo-perfused (96±27.9 ml/100 ml/min) myocardial segments (p<0.001). Overall, moderate correlation was observed between absolute MBF quantification at dynamic perfusion CT and the upslope of the perfusion CT-derived signal intensity over time curves (r = 0.47, p<0.01). Correlation between MBF and semiquantitative upslope values was also moderate for hypo-perfused (r = 0.41, p<0.01) and normal myocardial segments (r = 0.43, p<0.01).
### Table 1. Patient demographics.

<table>
<thead>
<tr>
<th>Population</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>10</td>
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<tr>
<td>Age (years) (mean±SD; range)</td>
<td>62.7±7.1 (51-71)</td>
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<td>Gender (M/F)</td>
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<th>Heart rate (bpm) (mean±SD; range)</th>
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<td>Rest CT</td>
<td>63±12.1 (53-95)</td>
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<tr>
<td>Stress CT</td>
<td>75.3±16.7 (55-102)</td>
</tr>
<tr>
<td>Rest MRI</td>
<td>61.2±11.7 (50-89)</td>
</tr>
<tr>
<td>Stress MRI</td>
<td>69.2±11.8 (52-90)</td>
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<td>No known coronary artery disease</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>4 (40%)</td>
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<tr>
<td>PTCA without stent placement</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>PTCA with stent placement</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Bypass</td>
<td>2 (20%)</td>
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<table>
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<th>Cardiovascular risk factors</th>
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<tr>
<td>Hypertension (%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>3 (30%)</td>
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<tr>
<td>Family history (%)</td>
<td>4 (40%)</td>
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<tr>
<td>BMI (kg/m²; mean±SD; range)</td>
<td>30.8±5.6 (25.1-41.5)</td>
</tr>
</tbody>
</table>

SD: standard deviation; bpm: beats per minute; PTCA: percutaneous transluminal coronary angioplasty; BMI: body mass index.

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**Fig. 0**

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Fig. 0: 66 year-old woman with hypertension, dyslipidemia, and chest pain. (A) Volume rendered coronary CT angiography study. Curved multiplanar reformats of the RCA (B) and LAD (C) show eccentric calcification of the LAD but no significant stenosis. Dynamic stress perfusion CT (D) as well as stress MRI (E) show normal myocardial perfusion. The CT myocardial perfusion map (F) reveals homogenous myocardial perfusion. Delayed acquisition MRI study (G) does not show late enhancement of the myocardium.

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**Fig. 0:** 64 year-old man with history of smoking, hypertension, dyslipidemia, and prior inferior myocardial infarction treated with percutaneous transluminal coronary angioplasty. Curved multiplanar reformats of the LAD (A), Cx (B) and RCA (C) show extensive atherosclerotic disease with distal RCA occlusion (arrow in C). Visual assessment of dynamic CT perfusion (D) reveals inferior and inferoseptal perfusion defects (arrowheads), confirmed by MRI (E). Absolute MBF images (F, G) map the perfusion defects visualized during first-pass perfusion (arrowheads), which correspond to the known chronic inferior myocardial infarction with inferoseptal peri-infarct ischemia, as established by delayed enhancement CT (H, arrowheads) and MRI (I, arrowheads).

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**Fig. 0:** 51 year-old man with past history of inferoseptal myocardial infarction and prior RCA stent placement. (A) Curved multiplanar reformat of the RCA shows non-calcified plaque causing luminal irregularities (arrow) of the proximal RCA, two patent stents, and significant stenosis (arrowhead) of the RCA segment between the two stents. The CT myocardial blood pool perfusion map (B) reveals hypoperfusion of the basal inferior, inferoseptal and septal myocardial segments (arrows) consistent with fixed defects corresponding to chronic infarction and septal peri-infarct ischemia. Visual assessment of stress dynamic CT perfusion (C) and stress MRI (D) show hypo-perfusion in the ischemic and infarcted territory (arrows). Semi quantitative analysis results in comparable myocardial perfusion curves for CT (E) and MRI (F) in septal myocardium with reversible ischemia (dashed lines) and healthy lateral myocardium (solid lines), confirmed by delayed enhancement CT (G) and MRI (H).
**Fig. 0:** Differences in the upslope of the signal intensity over time curve mean values between healthy and diseased myocardium as assessed by stress perfusion CT (A) and MRI (B). Significant differences were observed in myocardial signal intensity upslope values between normal and hypo-perfused myocardium both with CT (5.4±2.1 SI/s vs. 4.4±1.5 SI/s) and MRI (5.1±2.2 SI/s vs. 3.8±2 SI/s). Error bars represent 95% confidence interval for the mean.
Table 2. Comparison of stress-induced myocardial perfusion upslope of the signal intensity over time curve between dynamic CT perfusion and MRI.

<table>
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<th>CT</th>
<th>MRI</th>
<th>p</th>
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<tr>
<td>Overall</td>
<td>5.2±2</td>
<td>4.8±2.3</td>
<td>0.07</td>
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<tr>
<td>Non-ischemic myocardium</td>
<td>5.4±2.1</td>
<td>5.1±2.2</td>
<td>0.23</td>
</tr>
<tr>
<td>Ischemic myocardium</td>
<td>4.4±1.5</td>
<td>3.8±2</td>
<td>0.11</td>
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</table>

Fig. 0

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**Fig. 0:** Bland-Altman analysis comparing agreement between stress CT and MRI derived upslope of the signal intensity over time curves.

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Conclusion

We demonstrate that adenosine-stress dynamic perfusion CT is technically feasible and can differentiate between healthy, diseased, and at risk myocardium. This technique enables semi quantitative assessment of perfusion parameters in a comparable fashion as MRI. Dynamic perfusion CT shows particular promise for the absolute quantification of MBF, although still in moderate correlation with the upslope of the signal intensity over time curve. These findings may serve to further emphasize the potential of CT for integrative imaging of all pertinent aspects of coronary heart disease, including coronary artery morphology, cardiac function, perfusion, and viability with a single modality.
Fig. 0

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References


Personal Information

Gorka Bastarrika

Department of Radiology
Clínica Universidad de Navarra
Avenida Pío XII, 36
31008 Pamplona
SPAIN

If you have any query or you want to make any comment on this scientific exhibit please do not hesitate to contact us at:

bastarrika@unav.es

schoepf@musc.edu