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MISCELLANEOUS

Normal Reference Ranges for Echocardiography: rationale, study design, and methodology (NORRE Study)

Patrizio Lancellotti[1]*, Luigi P. Badano[2], Roberto M. Lang[3], Natela Akhaladze[4], George D. Athanassopoulos[5], Daniele Barone[6], Monica Baroni[7], Nuno Cardim[8], Jose Juan Gomez de Diego[9], Genevieve Derumeaux[10], Raluca Dulgheru[1], Thor Edvardsen[11], Maurizio Galderisi[12], Alexandra Gonçalves[13], Gilbert Habib[14], Andreas Hagendorff[15], Krasimira Hristova[16], Seisyou Kou[1], Teresa Lopez[17], Julien Magne[1], Gonzalo de la Morena[18], Bogdan A. Popescu[19], Martin Penicka[20], Tolga Rasit[21], Jose David Rodrigo Carbonero[22], Alessandro Salustri[23], Nico Van de Veire[24], Ralph Stephan von Bardeleben[25], Dragos Vinereanu[26], Jens-Uwe Voigt[27], Damien Voilliot[1], Jose Louis Zamorano[28], Erwan Donal[29], and Gerald Maurer[30]

[1]University of Liège Hospital, GIGA Cardiovascular Science, Heart Valve Clinic, Liege, Belgium; [2]Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Via Giustiniani 2, 35123 Padua, Italy; [3]Department of Medicine, University of Chicago Medical Center, Chicago, IL, USA; [4]Echocardiography Laboratory of Adult Cardiology, Department of the JOANN Medical Center, Tbilisi, GA, USA; [5]Echocardiology Department, Onassis Cardiac Surgery Center, Athens, Greece; [6]Laboratory of Cardiovascular Ecography, Cardiology Department, S. Andrea Hospital, La Spezia, Italy; [7]Laboratorio Di Ecocardiografia Adulti, Fondazione Toscana 'G.Monasterio' - Ospedale Del Cuore, Massa, Italy; [8]Echocardiography Laboratory, Hospital da Luz, Lisbon, Portugal; [9]Unidad de Imagen, Cardiovascular, ICV, Hosptial Clinico San Carlos, Madrid, Spain; [10]Department of Cardiology, Paris, France; [11]Department of Cardiology, Institute for Surgical Research and Center for Cardiological Innovation, Oslo University Hospital, Rikshospitalet, Oslo, Norway; [12]Department of Clinical and Experimental Medicine, Federico II University Hospital, Naples, Italy; [13]Cardiology Department, University of Porto Medical School/Centro Hospitalar S. João, Porto, Portugal; [14]Cardiology Department, Hôpital La Timone, Aix-Marseille University, 13284 Marseille, France; [15]Echokardiographie-Labore des Universitätsklinikums AöR, Department of Cardiology-Angiology, University of Leipzig, Leipzig, Germany; [16]Department of Noninvasive Functional Diagnostic and Imaging, University National Heart Hospital, Sofia, Bulgaria; [17]Cardiology Department, La Paz Hospital, Madrid, Spain; [18]Unidad de ImagenCardiaca. Servicio de Cardiologia, Hospital UniversitarioVirgen de la Arrixaca, Murcia, Spain; [19]'Carol Davila' University of Medicine and Pharmacy, Euroecolab, Institute of Cardiovascular Diseases, Bucharest, Romania; [20]Cardiovascular Center Aalst, OLV-Clinic, Aalst, Belgium; [21]EkokardiografiLaboratuarı, AmerikanHastanesi, Istanbul, Turkey; [22]Laboratorio de Ecocardiografia Hospital de Cruces, Barakaldo, Spain; [23]SheikhKhalifa Medical City, Abu Dhabi, United Arab Emirates; [24]Echocardiography Unit, AZ Maria Middelares, Gent, Belgium; [25]Medical Department Cardiology, Universitätsmedizin of the Johannes Gutenberg-University Mainz, Mainz, Germany; [26]Cardiovascular Research Unit, University and Emergency Hospital, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania; [27]Echocardiography Laboratory, Department of Cardiovascular Diseases, University Hospital Gasthuisberg, Leuven, Belgium; [28]Research Hospital Institution, Servicio Madrileño de Salud, Madrid, Spain; [29]Service de Cardiologie, CHU RENNES, CIC-IT 804 &LTSI, INSERM U 1099, Université Rennes-1, Rennes, France; and [30]Department of Cardiology, Medical University of Vienna, Vienna, Austria

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Background Availability of normative reference values for cardiac chamber dimensions, volumes, mass, and function is a prerequisite for the accurate application of echocardiography for both clinical and research purposes. However, due to the lack of consistency in current echocardiographic 'reference values', their use for clinical decision-making remains questionable.

Aims The aim of the 'Normal Reference Ranges for Echocardiography Study (NORRE Study)' is to obtain a set of 'normal values' for cardiac chamber geometry and function in a large cohort of healthy Caucasian individuals aged over a wide range of ages (25–75 years) using both conventional and advanced echocardiographic techniques.

Methods The NORRE Study is a large prospective, observational multicentre study in which transthoracic echocardiographic studies will be acquired in 22 laboratories accredited by the European Association of Cardiovascular Imaging and in one laboratory in the USA accredited by ICAEL. The final sample size has been estimated in 1100 normal subjects in whom M-mode, 2D, and 3D imaging, colour Doppler, pulsed-wave Doppler, pulsed-wave tissue Doppler, and colour

* Corresponding author: Department of Cardiology, University Hospital SartTilman, B - 4000 Liege, Belgium. Tel: + 32 4 366 71 94; fax. +32 4 366 71 95, Email: plancellotti@chu.ulg.ac.be

tissue Doppler imaging data will be obtained. All studies will be sent to a central echocardiographic core laboratory for quantitative analysis. Multiple studies will be performed for reproducibility analysis.

Conclusion After completion of the NORRE Study, uniform reference limits according to age, gender, and anthropometric parameters will be available to standardize the quantitative interpretation of echocardiography.

Keywords M-mode • 2D and 3D echocardiography • Cardiac mechanics • Chamber size and function • reference values

Rationale

Echocardiography is the most widely used cardiac imaging technology in the clinical setting.[1] It is estimated that >20 billion echocardiograms are performed each year in the USA. A substantial increase in the utilization of this powerful investigative tool has been noted in recent years.[2]

The clinical usefulness of echocardiography is based on the detection of abnormalities, which in fact rely on the accurate definition of 'normality'.[3–6] Although qualitative echocardiographic interpretation provides helpful information for the practicing clinician, quantitative echocardiography plays a momentous role in the diagnosis, treatment, and prognostication. Furthermore, the definition of 'normal values' including 'normal ranges' according to age, gender, and body surface area is of critical importance for the optimal application of clinical echocardiography.[7–9] Currently, available echocardiographic 'reference values' that define 'normality' are mostly based on cross-sectional observations and refer to earlier studies with wide variability of sample sizes, selection criteria, definition of 'healthy individuals', performance and/or reading approaches, or statistical analyses, and often obtained using old technologies.[1,3–11] Owing to the lack of consistency in echocardiographic 'reference values', the use of these published 'reference limits' for clinical decision-making remains questionable. Hence, although standardization on obtaining and performing echocardiographic measurements has been highlighted through the certification and laboratory accreditation process in Europe, there is still an urgent need for standardizing the interpretation of cardiac echocardiographic measurements.[12,13] Moreover, with the advent of new methodologies such as tissue Doppler imaging, 2D speckle tracking for myocardial deformation, and 3D echocardiography, it is likely that the current reference values generated using M-mode echocardiography and 2D echocardiography have become clinically questionable. Furthermore, the applicability of these new technologies into routine clinical practice requires the development of reference limits.[14–19] The Normal Reference Ranges for Echocardiography Study (NORRE Study) aims to prospectively provide a set of 'normal values' in a large cohort of healthy individuals over a wide range of ages (25–75 years old) using both conventional and advanced echocardiographic techniques. In the present report, we describe the study rationale, study design, methodology, and potential impact of the NORRE Study.

The NORRE Study

The NORRE Study is a large prospective multicentre study performed in 22 laboratories accredited by the European Association of Cardiovascular Imaging (EACVI) and in one American laboratory accredited by ICAEL to perform transthoracic studies. Each participating laboratory will be required to enrol 50 patients (50% males, 10 for each age decade: 25–35, 36–45, 46–55, 56–65, 66–75) for a final sample size of 1100 normal subjects. Only healthy volunteers who satisfy all inclusion/exclusion criteria will be included in the final study analysis. Enrolment will start in February 2013 and will be concluded by early August 2013. All participating centres will perform comprehensive echocardiographic examinations including conventional and advanced imaging.

Inclusion and exclusion criteria for the study

The study group will consist of adults with technically adequate echocardiograms. Healthy adult Caucasian volunteers aged ≥25 years with normal physical cardiac examination (with no systolic nor diastolic murmur), normal ECG, no cardiovascular risk factor associated with a risk score >10%, without a history of any cardiovascular disease or any systemic diseases known to affect the cardiovascular system, no chronic excessive alcohol consumption, not currently on medical therapy with cardio-active drugs, and no structural heart disease on echocardiography will be prospectively recruited. Exclusion criteria will also include trained athletes, pregnancy, or body mass index >30 kg/m^2.

Clinical data and blood sample

In all centres, clinically screened subjects will undergo a blood test to measure glycaemia, cholesterol level, and renal function (Table 1). Any recent laboratory results obtained within 3 months of the echocardiographic study will be considered valid. Before the echocardiographic examination, measurements of

Table 1: Demographic and biological data

Data
Age (years)
Sex
Height (cm)
Weight (kg)
Waist measurement (cm)
Systolic/diastolic blood pressure (mmHg)
Glycaemia (mg/dL)
Cholesterol level (mg/dL)

Table 2: Echocardiographic views, tracings, and data sets

Parasternal long-axis viewz	**Parasternal short-axis view**
M-mode	
M-mode of the LV as close as possible to the minor axis of the LV avoiding papillary muscles	2D view of the aortic valve level
M-mode of the aortic valve and the left atrium	2D view at the basal level (>50–70 fps)
M-mode of the ascending aorta	2D view at the mid-ventricular level (>50–70 fps)
2D image/colour Doppler	2D view at the apical level (>50–70 fps)
View optimized for the aortic root	2D View at the great vessel level (for RVOT diameter measurement)
Optimized zoomed view for the aortic root (for LVOT diameter measurement)	PW Doppler RVOT
View optimized for the ascending aorta	Colour flow Doppler to eliminate > mild valve regurgitation
2D image of the LV and the mitral valve	Subcostal View
Colour flow Doppler of the aortic valve and the mitral valve to exclude >mild valve regurgitation	Subcostal view optimized for the RV wall thickness
	2D image of the inferior vena cava while asking the subject to 'sniff'
Apical 4-chamber view	**Apical 4-chamber view**
View optimized for the LV (>50–70 fps). Avoid foreshortening of the image by maximizing the length of the LV cavity and avoiding the papillary muscle. Always obtain the widest possible LV cavity to ensure optimal assessment of LV volumes	PW Doppler trans-mitral inflow velocity with the sample volume positioned at the mitral tips
Colour flow Doppler to exclude any regurgitation > mild	PWD mitral inflow + LV outflow for IVRT measurement
Continuous wave (CW) Doppler mitral regurgitation	View optimized for both atria (>50–70 fps)
Colour TDI (FR >110 fps) with focus on the LV	Colour TDI (FR >110 fps) with focus on both atria
PW TDI basal septum	View optimized for the right ventricle (>50–70 fps)
PW TDI basal lateral	Colour TDI (FR >110 fps) with focus on the RV
PW TDI lateral RV	PWD tricuspid inflow (increase the size of the sample volume to optimize tracings)
TAPSE tracing	CW Doppler tricuspid regurgitation
Apical 2-chamber view	**Apical 5-chamber view**
View optimized for the left ventricle (>50–70 fps). Avoid foreshortening of the view by obtaining the longest possible major axis displayed and the widest cavity	Colour flow to evaluate any aortic regurgitation
View optimized for the left atrium (>50–70 fps)	PW Doppler at the LVOT. Place the sample volume within 1 cm of the aortic valve in the LVOT
Colour TDI 2CH (FR >110 fps) with focus on the left atrium	CW Doppler across the aortic valve
Colour flow Doppler to evaluate any mitral regurgitation >Mild	**Apical 3-chamber view**
PW TDI basal inferior	View optimized for the left ventricle (>50–70 fps). Avoid foreshortening of the view by obtaining the longest and the widest possible LV cavity area
PW TDI basal anterior	Colour TDI 3CH (FR > 110 fps) with focus on the left atrium
3D data acquisition	
For the LA (>20 vps); for the RA (>20 vps); for the LV (>20 vps); for the RV (>20 vps)	

CW, continuous wave; LA, left atrium; LV, left ventricular; OT, outflow tract; PW, pulsed-wave; RA, right atrium; RV, right ventricle; TDI, tissue Doppler imaging.

blood pressure, weight, height, and waist circumference will be performed. The body surface area will be calculated in all subjects. Blood pressure measurement will be performed after 10 min of rest in the supine position and before the echocardiographic examination. Demographic and biological data will be reported on a dedicated spreadsheet.

Echocardiographic examination

A comprehensive echocardiographic examination will be performed on all subjects with the use of either a Vivid E9 (GE Vingmed Ultrasound, Horten, Norway) and/or iE33 (Philips Medical Systems, Andover, USA) ultrasound systems according to a predetermined protocol (Table 2). All patients will be examined in the left lateral position using grey-scale second-harmonic imaging technique, with the adjustment of image contrast, frequency, depth, and sector size for an adequate frame rate and optimal LV border visualization. Image acquisition will be performed during held end-expiration to minimize cardiac respiratory motion. A minimum of at least three cardiac cycles will be recorded for analysis. M-mode, 2D (frame rates >50–70 fps), and 3D imaging, colour Doppler, pulsed-wave Doppler, pulsed-

wave tissue Doppler, and tissue Doppler imaging (frame rates $\geq$110 s $-$ 1) data will be obtained in all patients. Three LV short-axis views (basal, middle, and apical) and all standard LV apical views (4-, 2-, 3-chamber views) will be acquired. Care will be taken to ensure that the basal short-axis level includes the tip of the mitral valve leaflets and that the middle level short-axis view includes the tip of the papillary muscles. Care will be taken to avoid LV foreshortening in all apical views. To determine the timing of cardiac events, LV inflow and outflow velocities will be recorded using a pulsed-wave Doppler echocardiogram. Three-dimensional full-volume data sets (LV, right ventricle, left atrium, right atrium) will be obtained by stitching together 4 or 6 consecutive ECG-gated subvolumes. The 3D echocardiographic data sets will be acquired at the end of the standard 2D echocardiography.

Data management and collection

Standardization of image acquisitions were discussed at the Euro-echo and Other imaging modalities meeting organized by the EACVI in Athens, December 2012. A running phase was started in each centre in January 2013. Each laboratory will record a complete case that will be subsequently sent to the Echocardiographic Core Lab for quality control. After the completion of the run-in phase, all centres will be invited to begin subject recruitment in early February 2013. All echocardiographic and Doppler images will be recorded in a digital raw-data format (native DICOM format) and stored, after anonymization, on optical disks for off-line analysis at the core centre. All images will be centralized at the EACVI Central Core Laboratory at the University of Liège, Belgium.

Image analysis

Each centre will perform basic echocardiographic measurements according to previously published recommendations. Data were reported on a dedicated spreadsheet and transferred to the Core Lab. All measurements done on each site will be used for inter-observer variability and agreement. At the Core Lab, two EACVI observers (S.K., D.V.), blinded to the age and sex of each subject, will perform an image quality check and analysis. The image analysis will be performed sequentially according to the different echocardiographic modalities: (i) standard M-mode and 2D measurements; (ii) Doppler assessments (standard and tissue Doppler imaging); (iii) 3D evaluation of chamber volumes and function. In a second phase, advanced imaging analysis was performed for the assessment of cardiac mechanics using the speckle-tracking (STE) software from each company (EchoPAC BT 12, GE; QLAB, version 9, Philips).

Ethic committee

The NORRE Study will respect the ethical principles for conducting research on human subjects. The framework established for the NORRE activities will use the highest standards in an accredited laboratory. Protection of privacy with regard to processing of personal data will be ensured. The relevant institutional review boards will approve the protocol and all patients will give their written informed consent.

Statistical analysis

Continuous variables will be expressed as mean $\pm$ SD or median and inter-quartile range according to data distribution. Categorical variables will be reported as percentages. All statistical analyses will be carried out using SPSS version 17 (SPSS, Inc., Chicago, IL, USA). Julien Magne, the appointed EACVI statistician, will be in charge of the statistical analysis. Normal distribution of variables will be verified using the Kolmogorov–Smirnov test. Comparison between men and women will use the unpaired *t*-test. Quantile regression models will be used to model the relationship between age and pre-defined centiles of each measurement. Gender-specific models will be created. For morphological measurements, the effect of body composition will be explored. Reference limits will be estimated at 10-year age increments for men and women separately. Intra-observer and inter-observer variability will be assessed in 70 randomly selected subjects. Reliability will be assessed using Bland–Altman analysis and an intra-class correlation coefficient with the 95% confidence interval. $P < 0.05$ will be considered as statistically significant.

Discussion

Quantification of cardiac chamber size and function ranks among the most frequent requests in echocardiography for both clinical and research purposes.[20,21] The knowledge of cardiac dimensions and performance plays a critical role in patient management and these are powerful predictors of morbidity and mortality. Documentation of normative reference values for cardiac chambers, dimensions, volumes, mass, and function is thus a prerequisite for the accurate application of echocardiography in both the clinical setting and research trials.

The NORRE Study aims to establish normal reference limits for echocardiography in healthy Caucasian adults and to examine the influence of age, sex, and body size on the reference ranges. Several studies have proposed reference limits for 'normal' echocardiography, but these have been mainly based on heterogeneous observational populations or selected samples using dated echocardiographic techniques.[1,7,9] More recently, a few single-centre studies have attempted to provide normal reference ranges for echocardiography using new imaging technologies.[14,15,18] However, these studies have reported on only a limited number of patients or have mainly focused on a single echocardiographic modality. The NORRE Study will be the largest prospective European registry set up by the EACVI research committee and carried out in EACVI accredited laboratories. Both conventional and advanced imaging techniques will be obtained in all subjects. Reference values will also be obtained for Doppler and conventional M-mode and 2D measurements. All standard echocardiographic parameters will be evaluated (i.e. age-and sex-related size and function of all cardiac chambers, age-related values of mitral and tricuspid *E*/*e*′, height-related values of aortic root dimensions).

To the best of our knowledge, the NORRE Study will be the first registry reporting normative reference values for 3D

echocardiography in a large cohort of normal subjects. Three-dimensional echocardiography is now available in many centres in Europe. However, it is well known that reference values from conventional 2D echocardiography cannot be used interchangeably with 3D parameters.[19] Hence, the availability of age- and gender-specific reference values for 3D echocardiography should facilitate implementation of this technology in the clinical routine.

STE provides assessment of cardiac chamber function through the largely angle-independent quantification of myocardial deformation.[22] STE has shown value in quantitatively identifying global and regional dysfunction in a variety of cardiac conditions. However, one of the current limitations of strain imaging techniques is the lack of normal references limits according to age and sex in a large cohort of Caucasian subjects. In the second phase of the NORRE Study, the assessment of STE will be specifically addressed in order to identify thresholds of normality. The assessment of cardiac mechanics will also take place in this second phase. Cardiac rotation, torsion, and twist will be evaluated using each vendor-specific platform. Feasibility and reference limits will be provided for each parameter using 2D and 3D data sets.

Substudy analysis

In the NORRE Study, two echocardiographic systems, namely Vivid E9 and iE33, will be used. About one-half of the recruited subjects will be examined using both machines. Although the primary goal of the study is not to examine vendor-specific differences, a substudy analysis will compare the 2D and 3D results obtained with each vendor-specific platform. It is assumed that no significant differences will be found between vendors with respect to conventional 2D and 3D volumes and function parameters. In a second step, inter-vendor agreement for STE and cardiac mechanics will also be evaluated for each age and sex category. To finalize the second phase of the NORRE Study, all data sets will be imported onto the Image-Arena version 4.5 (TomTec Imaging Systems, Unterschleissheim, Germany) for complementary analysis in a neutral platform.

Future perspectives

The data collected in the NORRE Study offer the opportunity of representing a large database on normal subjects that will be then used as a reference for comparison with age-matched patients. Centralization of all echocardiographic studies in a native raw-data format in the EACVI Core Lab may serve ultrasound companies to test new algorithm software for volume or cardiac mechanics assessment.

Limitations

As the NORRE Study will only focus on healthy Caucasian volunteers, its results will not be transposable to Asian or African populations. Similarly, as only two imaging vendors will be used, the reference values obtained in the NORRE Study, especially for STE, will only be valid for GE and Philips machines. However, using a neutral platform, namely TomTec Imaging Systems, a common algorithm for strain analysis will be used allowing obtaining a set of reference values for STE in the whole cohort of patients.

Conclusion

The NORRE Study is the first European research project carried out by the EACVI. Thanks to the NORRE Study, development, and adoption of uniform reference limits according to age, gender, and anthropometric parameters will serve to standardize the quantitative interpretation of echocardiography. The availability of reference values in young to middle-aged and elderly subjects will enable us to strengthen the value of echocardiography in both clinical and research cardiology.

Project leaders and steering committee

Project Manager: P.L.; Project co-leaders: L.P.B. and R.M.L.; Steering committee: E.D. (Chair), T.E., G.D., M.G., A.G., G.H., P.L., J.M., G.M., B.A.P., J.L.Z. EACVI Research Committee supervised the protocol development, conduct of the study, analysis and presentation of the results.

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IMAGE FOCUS

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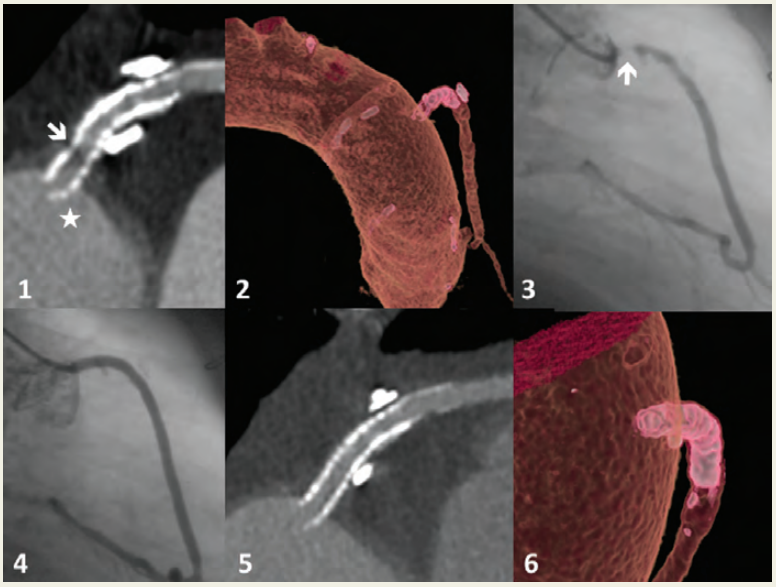
Coronary graft angioplasty guided by MSCT: an unexpected ostial stent deformation

David Pesenti Rossi[1]*, Christophe Caussin[2], Nicolas Baron[1], Thierry Fourme[1], and Bernard Livarek[1]

[1]Department of Cardiology, Versailles and Rambouillet Hospital, 177, rue de Versailles, Le Chesnay 78150, France and [2]Department of Cardiology, Marie Lannelongue Hospital, Le Plessis Robinson, France

* Corresponding author. Tel: +33 139638867; fax: +33 981709491. Email: david.pesentirossi@gmail.com

A 76-year-old man with a history of two-vessel coronary artery bypass grafting was admitted with recurrent angina. The proximal anastomosis of the left anterior descending (LAD) bypass grafting was directly stented with a bare-metal stent 2 years before.



Conventional angiography was performed, but selective LAD bypass catheterization failed. In this case of aortic stent protrusion, repeat catheterization of the ostium was difficult. Moreover, this bypass was located at the level of the aortic arch. A multi-slice computed tomography (MSCT) was performed (*Panel* 1) and revealed an ostial stent deformation (star) with a significant in-stent restenosis (arrow) of the LAD bypass proximal anastomosis. MSCT was able to identify an ostial stent deformation which can explain the catheterization failure. Then, the choice and the orientation of the catheter were guided by the MSCT 3D reconstructions (*Panel* 2, see Supplementary data online, *Video S1*). Coronary angiography confirmed a severe in-stent restenosis (*Panel* 3, arrow) of the proximal anastomosis. After predilatation, a drug-eluting stent was implanted with aortic protrusion and an angiographically adequate result (*Panel* 4). At 1-year follow-up, a repeat MSCT revealed an ideal stent position with aortic protrusion, an adequate expansion and no restenosis (*Panels* 5 and 6, see Supplementary data online, *Video S2*).

In the case of restenosis and aortic stent protrusion, repeat catheterization of the ostium was challenging. MSCT was a valuable tool for aorto-ostial lesion analysis and helped the operator to identify the catheterization difficulties.

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.