Eur J Nucl Med Mol Imaging (2008) 35:851–885
DOI 10.1007/s00259-007-0694-9

GUIDELINES

# EANM/ESC guidelines for radionuclide imaging of cardiac function

**B. Hesse · T. B. Lindhardt · W. Acampa · C. Anagnostopoulos · J. Ballinger · J. J. Bax · L. Edenbrandt · A. Flotats · G. Germano · T. Gmeiner Stopar · P. Franken · A. Kelion · A. Kjaer · D. Le Guludec · M. Ljungberg · A. F. Maenhout · C. Marcassa · J. Marving · F. McKiddie · W. M. Schaefer · L. Stegger · R. Underwood**

Published online: 26 January 2008


**Abstract** Radionuclide imaging of cardiac function represents a number of well-validated techniques for accurate determination of right (RV) and left ventricular (LV) ejection fraction (EF) and LV volumes. These first European guidelines give recommendations for how and when to use first-pass and equilibrium radionuclide ventriculography, gated myocardial perfusion scintigraphy, gated PET, and studies with non-imaging devices for the evaluation of cardiac function. The items covered are presented in 11 sections: clinical indications, radiopharmaceuticals and dosimetry, study acquisition, RV EF, LV EF, LV volumes, LV regional function, LV diastolic function, reports and image display and reference values from the literature of RVEF, LVEF and LV volumes. If specific

B. Hesse (✉) · A. Kjaer · J. Marving
Department of Clinical Physiology and Nuclear Medicine,
University Hospital of Copenhagen,
Rigshospitalet,
Copenhagen, Denmark
e-mail: bhesse@rh.hosp.dk

T. B. Lindhardt
Department of Cardiology, Hilleroed Hospital,
Hilleroed, Denmark

W. Acampa
Department of Biomorphological and Functional Sciences,
Institute of Biostructure and Bioimages of the National
Council of Research, University of Naples Federico II,
Naples, Italy

C. Anagnostopoulos · A. F. Maenhout
Department of Nuclear Medicine, Royal Brompton Hospital,
London, UK

J. Ballinger
Department of Nuclear Medicine,
Guy's Hospital–Guy's and St. Thomas' Foundation Trust,
St. Thomas Street,
London, UK

J. J. Bax
Department of Cardiology, Leiden University Medical Center,
Leiden, The Netherlands

L. Edenbrandt
Department of Clinical Sciences, Malmö, Lund University
Research Program in Medical Informatics,
Malmö University Hospital,
Malmö, Sweden

A. Flotats
Nuclear Medicine Department,
Autonomous University of Barcelona,
Hospital de la Santa Creu i Sant Pau,
Barcelona, Spain

G. Germano
Artificial Intelligence Program at Cedars-Sinai Medical Center
and Department of Medicine of the University of California at
Los Angeles,
Los Angeles, USA

T. G. Stopar
Department of Nuclear Medicine,
University Medical Centre Ljubljana,
Radiopharmacy and Clinical Biochemistry,
Ljubljana,
Zaloska 7, Slovenia

P. Franken
Nuclear Medicine, AZ VUB,
Brussels, Belgium

recommendations given cannot be based on evidence from original, scientific studies, referral is given to "prevailing or general consensus". The guidelines are designed to assist in the practice of referral to, performance, interpretation and reporting of nuclear cardiology studies for the evaluation of cardiac performance.

**Keywords** Nuclear imaging · EANM/ESC guidelines · Cardiac function

**Abbreviations**

| | |
|---|---|
| ACD | acid citrate dextrose |
| CAD | coronary artery disease |
| cMRI | cardiac magnetic resonance imaging |
| ECG | electrocardiogram |
| ECT | Emory Cardiac Toolbox |
| ED | end-diastolic |
| EDV | end-diastolic volume |
| ES | end-systolic |
| EF | ejection fraction |
| ERNV | equilibrium radionuclide ventriculography |
| ESV | end-systolic volume |
| FP | first pass |
| FPRNV | first-pass radionuclide ventriculography |
| HSA | human serum albumin |
| i.v. | intravenous |
| LAO | left anterior oblique |
| LBBB | left bundle branche block |
| LEGP | low energy general purpose |
| LEHR | low energy high resolution |
| LEHS | low energy high sensitivity |
| LPO | left posterior oblique |
| LV | left ventricle |
| LVV | left ventricular volume |
| LVEF | left ventricular ejection fraction |
| MI | myocardial infarction |
| MPS | myocardial perfusion scintigraphy |
| NSTEMI | non-ST elevation acute myocardial infarction |
| PFR | peak filling rate |
| $PFR_{SV}$ | PFR normalised to stroke volume |
| QGS | quantitative gated SPECT |
| RAO | right anterior oblique |
| RBC | red blood cells |
| RNV | radionuclide ventriculography |
| ROI | region-of-interest |
| RV | right ventricle |
| STEMI | ST elevation acute myocardial infarction |
| TAC | time–activity curve |
| TID | transient ischaemic dilatation |
| TPFR | time to peak filling rate |
| WM | wall motion |
| WTh | wall thickening |

## Preamble

The European guidelines for radionuclide imaging of cardiac function have been developed under the auspices of the European Council on Nuclear Cardiology (the joint group of the Cardiovascular Committee of the European Association of Nuclear Medicine and of the Working Group on Nuclear Cardiology of the European Society of Cardiology). The aim of the authors has been to present the state-of-the-art applications and protocols approved by experts in the field and to disseminate this information to the European nuclear cardiology community. The guidelines are designed to assist physicians and other healthcare

A. Kelion
Nuclear Medicine Department, Harefield Hospital,
Harefield, Middlesex, UK

D. Le Guludec
Service de medecine nucleaire, hôpital Bichat, APHP,
Université Denis-Diderot, UMR577B, and Inserm U773,
Paris, France

M. Ljungberg
Medical Radiation Physics, Clinical Sciences,
Lund, Lund University,
Lund, Sweden

C. Marcassa
Department of Cardiology, Fondazione Maugeri, IRCCS,
Veruno, Italy

F. McKiddie
Nuclear Medicine Department, Aberdeen Royal Infirmary,
Foresterhill Aberdeen,
Scotland, UK

W. Schaefer
Nuclear Medicine Department, University Hospital,
Aachen University of Technology,
Aachen, Germany

L. Stegger
Department of Nuclear Medicine, University Hospital Münster,
Münster, Germany

R. Underwood
Department of Nuclear Medicine, Royal Brompton Hospital,
London, UK

professionals in referring to, performing, interpreting and reporting the different radionuclide imaging examinations dealing with cardiac function.

It has been our intention to present information specifically adapted to European practice, based on evidence from original scientific studies. Where more than one solution seems to be practised, and none has been shown to be superior to the others, we hope that we have succeeded in specifically expressing this state of knowledge.

The authors comprise scientists from many different countries, all with sub-speciality expertise in nuclear cardiology. Every effort has been made to avoid conflicts of interest arising from non-academic and non-clinical relationships.

## List of contents



## 1. Clinical indications

### Introduction

Assessment of left ventricular (LV) function and volumes is important for prognostification, being very powerful predictors of long-term outcome after acute myocardial infarction (MI) [1, 2]. The information obtained to that obtained by ungated myocardial perfusion scintigraphy (MPS) by the addition of gating has been demonstrated in several studies to be of high clinical value. The assessment of the function of the right ventricle (RV) is recognised to be important in subgroups of patients including arrhyhmogenic RV, in lung transplant candidates, and after MI, possibly including RV infarction, with high prognostic value of demonstrating RV dysfunction. Determination with equilibrium radionuclide ventriculography (ERNV) of LV ejection fraction (LVEF) is recognised as one of the methods-of-choice for monitoring of cardiotoxicity of cytotoxic drugs [3].

The use of radionuclide imaging was addressed in the ACC/AHA/ASNC practice guidelines [4], a report from the three major US organizations involved in this field. In this report, the main focus is on MPS, but assessment of LV function is closely related to that. The ACC/AHA/ASNC classifications I, II and III have been used to summarise the indications as follows:

1. Class I: Conditions for which there is evidence and/or general agreement that a given procedure (or treatment) is useful and effective
2. Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure

   Class IIa: Weight of evidence is in favour of usefulness/efficacy

   Class IIb: Usefulness/efficacy is less well established by evidence/opinion
3. Class III: Conditions for which there is evidence and/or general agreement that the procedure is not useful or effective and, in some cases, may be harmful. Such indications are not discussed in the present guideline

*Levels of evidence* for individual class assignments are designated as:

– A = data derived from multiple, randomised, clinical trials
– B = data derived from a single, randomised trial or from non-randomised studies
– C = consensus opinion of experts

Level A is rarely available for diagnostic imaging and level B sometimes; hence, level C is most often applied.

In the present guidelines, emphasis has been laid on the presentation of evidence-based data with direct references to original papers. Clinical indications may often depend on several local factors such as availability, experience, traditions, reimbursement, risk of complications, logistics, etc. Furthermore, new modalities or development within a modality [gating of MPS, cardiac CT, contrast MRI (cMRI), echocardiography, plasma atrial and brain natriuretic peptides (ANP and BNP)] may have a great impact on the clinical indications for alternative techniques. The most important indications are listed in Table 1.

### Prognosis after acute MI with ST elevation

The prognosis of patients after ST elevation acute myocardial infarction (STEMI) is mainly determined by infarct size, residual myocardium at risk (myocardial ischaemia) and LVEF. Radionuclide imaging provides the information on all these three components. Particularly when pharmacological stress is used, radionuclide studies can be

**Table 1** Clinical indications

| Indications | Recommended radionuclide method | US classification and level |
|---|---|---|
| LV function after STEMI | Gated rest MPS | I B |
| LV function after NSTEMI and in unstable angina | Gated rest MPS | I B |
| RV function after AMI | FP RNV | II B |
| Diagnosis of chronic CAD in intermediate likelihood risk | Gated stress MPS | I B |
| Diagnosis of chronic CAD in patients unable to exercise | Gated pharmacological stress MPS | I B |
| Diagnosis of chronic CAD in patients undergoing non-cardiac major surgery and intermediate or high risk likelihood of CAD | Gated exercise or pharmacological stress MPS | I B |
| Ischaemic heart failure | Gated rest MPS (+FP) | I A |
| Chemotherapy monitoring (anthracyclines, etc.) | ERNV | I A |
| Arrhythmogenic RV | FP RNV or tomo ERNV | IIa B |
| Aortic regurgitation: LVEF monitoring | ERNV or gated MPS | I A |
| Before heart transplantation | ERNV or gated MPS | – |
| Monitoring after heart transplantation | ERNV or gated MPS | – |
| Before lung transplantation | FP RNV | – |

Recommended methods in major clinical indications for nuclear cardiology functional imaging. For the explanation of the abbreviations, see abbreviation list (before Section 1).

performed safely already 2–4days after infarction [5]. This approach has recently been confirmed in the prospective, randomised INSPIRE Trial (adenosine Sestamibi SPECT post-infarction evaluation) [2]: 728 clinically stable survivors of MI were enrolled and underwent adenosine-gated MPS (with $^{99m}$Tc-sestamibi) within 10days of hospital admission. The patients had 1year follow-up. Based on stress perfusion defect size, the extent of ischaemia and LVEF, the patients were stratified into high, intermediate, and low-risk groups. The low-risk group, in particular, had a death/reinfarction rate <2%.

It is strongly believed, although not directly documented, that the integration of perfusion and function yields superior risk stratification after MI. The assessment of RV function in patients with suspected RV infarction is also of strong prognostic value.

In patients with acute MI without ST elevation (NSTEMI) or unstable angina, assessment of ischaemia is most important, but assessment of LV function has also been recognised to provide important information.

## Known or suspected coronary artery disease: diagnosis and prognosis

The role of radionuclide imaging in the detection of coronary artery disease (CAD) has been demonstrated to be cost-effective in many studies in patients with intermediate to high likelihood of CAD [6, 7]. In particular, gated MPS permits accurate diagnosis of CAD [8].

Similarly, the prognostic value of gated single-photon emission computed tomography (SPECT) imaging in patients with known or suspected CAD has been reported extensively; e.g. the work by Sharir et al. [9] has clearly demonstrated the incremental value of LV function/volume data over perfusion data alone for prognosis.

Patients with intermediate or high risk of CAD being evaluated before non-cardiac surgery are an important category. For these patients, the same applies as for symptomatic patients with known or suspected CAD.

## Heart failure: diagnosis and prognosis

The number of patients with heart failure has increased substantially, and the majority of patients suffer from ischaemic aetiology of heart failure. In these patients, prognosis is determined by LVEF, LV volumes, ischaemia and viability. RV function is also increasingly recognised as prognostic parameter. In patients with heart failure, initial assessment of LV and RV function is considered a class I indication.

Identification of patients who may benefit from an internal cardioverter defibrillator is another important issue: According to the MADIT-II results, patients with previous MI and LVEF ≤30% benefits from ICD implantation [10]. In these patients, accurate assessment of LVEF is indicated, and radionuclide imaging is one of the techniques that can provide this information.

### *Sub-populations without coronary disease*

In the subpopulations indicated below, LV and RV function is clinically indicated and radionuclide assessment can be performed. Although echocardiography is performed for the LV in many places, the radionuclide method is preferred for

the RV if more accurate measurements are needed. Also for LVEF monitoring purpose, the low inter-day variation of LVEF determined with ERNV makes this technique preferable compared with echocardiography for large patient groups (chemotherapy, treatment of multiple sclerosis, etc.).

- Dilated cardiomyopathy caused by cytotoxic cardiotoxicity ERNV is the method preferred in the special category of patients with risk of dilated cardiomyopathy caused by cardiotoxicity of cytotoxic drugs (doxorubicin, trastuzimab, etc.). After chemotherapy with these agents, a (cumulative) dose-dependent depression of LVEF and progressive heart failure may occur, usually partly reversible if chemotherapy is interrupted [11, 12].
- RV dysplasia. Arrhythmogenic right ventricular dysplasia is characterised by RV dilatation and depressed function and other markers of RV dysfunction [13].
- Chagas' myocarditis/cardiomyopathy. The disease is characterised by severe LV dilatation and dysfunction, and radionuclide assessment of LV function is often indicated.
- Aortic regurgitation. When LVEF falls below 55%, prognosis becomes worse, and valve replacement needs to be considered [14]. Initial and serial assessment of LV and RV function by radionuclide imaging is considered very useful.
- Candidates for cardiac resynchronisation therapy. In patients with reduced LVEF assessment of cardiac dyssynchrony, both inter- and intra-ventricular dyssynchrony, including phase analysis, may be important for evaluation for cardiac resynchronisation therapy (cf. section 9 on physics and software, parametric images).
- Candidates for and monitoring after heart transplantation. Accurate determination of LVEF is used for determination of the right time for referral to heart transplantation and for monitoring in post-transplant patients.
- Candidates for lung transplantation. Knowledge of RV dysfunction, including RVEF before lung transplantation, is an important parameter whether lung or heart–lung transplantation should be done.

## 2. Radiopharmaceuticals: dosimetry

### Introduction

Intravascular tracers, including $^{99m}$Tc-labelled erythrocytes (red blood cells, RBC) and $^{99m}$Tc-labelled human serum albumin (HSA), are used for radionuclide ventriculography (RNV). First-pass (FP) RNV can be performed with many other $^{99m}$Tc-labelled radiopharmaceuticals. Cardiac functional imaging can also be performed during gated MPS with the radiopharmaceuticals used and, preferably, with the $^{99m}$Tc-labelled perfusion tracers, although $^{201}$Tl-thallous chloride can be used [15]. Finally, gated PET cardiac imaging also allows evaluation of cardiac function.

### $^{99m}$Tc-labelled erythrocytes

Radiolabelling procedures should follow the European Association of Nuclear Medicine (EANM) guidelines on current Good Radiopharmacy Practice (cGRPP) in the Preparation of Radiopharmaceuticals.

#### *Pre-tinning*

Erythrocytes may be labelled with $^{99m}$Tc by in vivo, in vitro and combined in vivo/in vitro approaches [16–19]. The advantages and disadvantages of three different approaches are summarised in Table 2. The basic mechanism of the labelling in all approaches is the same: The RBCs are "pre-tinned" by stannous ($Sn^{2+}$) ions, which may be present in different compounds, followed by addition of $^{99m}$Tc-pertechnetate after 10–30min. The stannous agent diffuses into the cell and gets firmly bound to cellular components. The pertechnetate diffuses freely across the cell membrane. In the presence of $Sn^{2+}$ in the cell, it is reduced and subsequently binds to the beta chain of haemoglobin. Because free $Sn^{2+}$ ions are susceptible to hydrolysis and precipitation at physiological pH, they will be rapidly removed from the blood by the reticuloendothelial system. The stannous agent is, therefore, usually in a complex of a weak chelator, such as pyrophosphate or medronate, which prevents hydrolysis [19, 20]. The amount of $Sn^{2+}$ required for optimal labelling is in the range of 0.03 to 0.15mg/ml of blood or 10–20mg/kg body weight. Deviation from that range may reduce labelling efficiency by up to 20% [21].

#### *Labelling*

*In vivo labelling* This approach is the simplest and least time-consuming labelling technique. It involves an injection of a reconstituted solution of a $Sn^{2+}$ agent followed by injection of sodium $^{99m}$Tc-pertechnetate 20–30min later. The major disadvantage of the in vivo technique is a generally lower and more variable labelling efficiency. Low labelling yields may be because of insufficient $Sn^{2+}$ incorporation into the cell, low haemoglobin concentration and/or low haematocrit. When pertechnetate is reduced outside the RBC, it is not able to diffuse across the red cell membrane, resulting in a high-background activity.

*In vitro labelling* This should be performed under strictly aseptic conditions in a laminar airflow unit dedicated to cell labelling. A small volume (1–10ml) of blood, anticoagu-

**Table 2** Radiopharmaceuticals

| Labelling technique | Advantages | Disadvantages |
|---|---|---|
| $^{99m}$Tc-labelled RBC | | |
| In vivo labelling | Simple and rapid—no handling of blood | Incomplete labelling; higher background activity in tissues; cannot be used for volume determination; affected by haematocrit and haemoglobin concentration |
| In vitro labelling | Highest labelling efficiency and stability | Involves handling of blood; requires more technical expertise; more expensive and more time consuming |
| In vivo/in vitro labelling | Less cumbersome than in vitro labelling | Less efficient than in vitro labelling without the washing step; involves some handling of blood |
| $^{99m}$ Tc-labelled human serum albumin (HSA) | | |
| Commercial kit | Simple and rapid; single injection; no handling of blood | Some of the $^{99m}$Tc is cleared from circulation; cannot be used for volume determination; HSA is less stable in vivo as intravascular tracer (significant problem with LVEF monitoring over hours, etc.) |

Comparison of advantages and disadvantages of radiopharmaceuticals used for RNV. For the explanation of the abbreviations, see abbreviation list (before Section 1).

lated with heparin or acid citrate dextrose (ACD) solutions but not with ethylenediaminetetraacetic acid (EDTA) or oxalate, is incubated with an aliquot of a reconstituted $Sn^{2+}$ agent (1–50μg) for 5–10min in a closed vial to avoid exposure to atmospheric oxygen. When stannous citrate is used for pre-tinning of the RBCs (e.g. UltraTag [17]), the incubation is followed by the addition of 0.1% sodium hypochlorite and ACD solution, which results in oxidation of any excess $Sn^{2+}$ to $Sn^{4+}$. In this case, free Sn in the plasma may be removed as a Sn–citrate complex. After incubation, the cells are separated by centrifugation, the plasma is removed and the RBCs are incubated with $^{99m}$Tc-pertechnetate for 5–20min with occasional mixing. After incubation, unbound activity is washed away by addition of a few milliliters of saline and centrifugation. The supernatant is removed and the red cells resuspended in saline before re-injection. With the Ultratag method, the centrifugation steps are not required [17].

In vitro labelling gives by far the highest labelling efficiency and, over time, the most stable labelling. Measurement of erythrocyte volume by in vitro labelled RBCs with $^{99m}$Tc gives values similar to labelling with the gold standard $^{51}$Cr; this is not the case with the in vivo or in vivo/in vitro method nor with $^{99m}$Tc-labelled HSA (see below), calculated from total blood volume and haematocrit. Therefore, determination of absolute LV volumes with RNV must be performed using in vitro labelled RBCs.

*In vivo/in vitro labelling* The intravenous (i.v.) administration of a stannous agent is followed 15–30min later by withdrawal of an aliquot (3–10ml) of pre-tinned blood through a cannula into a shielded syringe containing an anticoagulant (ACD or heparin) and the required amount of $^{99m}$Tc-pertechnetate. The blood is mixed with the $^{99m}$Tc-pertechnetate and allowed to incubate for 10–20min at room temperature with occasional mixing. The unbound activity may be washed away by centrifugation before reinjection via the same cannula. Alternatively, the radiolabelled RBCs can be reinjected without the washing step.

*Administered activity* The usual administered activity is 800MBq (range of 500–1,050MBq) for adult patients [22]. The activity for children may be adjusted according to body weight, with a minimum activity of 80MBq to obtain images of sufficient quality [23].

*Administration* The $^{99m}$Tc-pertechnetate- or $^{99m}$Tc-labelled RBCs should be administered through a secure i.v. line in accordance with local radiation protection practices. For administration of $Sn^{2+}$ compounds, use of a teflon catheter or cannula should be avoided because the $Sn^{2+}$ can react with the catheter [24]. The stannous agent and $^{99m}$Tc-pertechnetate should not be given through the same cannula.

*Drug interactions* Patient medication can affect labelling of RBCs. Drugs may interfere with stannous ions so that stannous is not taken up by the cells, may affect the RBC membrane or may affect the target of binding by reducing the haematocrit and/or haemoglobin concentration. Reduction in RBC labelling yield has been reported with a number of drugs, some of the clinically most significant ones being anthracycline antineoplastics, e.g. doxorubicin and epirubucine [25]. A number of other interactions have been reported (for reviews, see [26, 27]).

*Radiation dosimetry* The radiation-absorbed doses to various organs in healthy subjects after administration of $^{99m}$Tc RBCs labelled in vivo or in vitro are given in ICRP 80 [28]. The effective dose after administration of 800MBq is 5.6mSv. The typical radiation absorbed doses for an adult to the critical organs (adrenals, heart, kidneys, liver and

spleen) are 8, 18, 14, 10 and 11mGy. For children, the modification of the administered activity according to the EANM dosage card assures an almost weight-independent effective dose [23].

*Pregnancy* A relative contraindication. Evaluation by other techniques such as echocardiography or MRI is preferred.

*Breast feeding* Breast feeding can be continued after in vitro labelling. When using in vivo labelled RBCs, it is considered necessary that breast-feeding be interrupted and the expressed feeds discarded because of the presence of free $^{99m}$Tc-pertechnetate, which is present in plasma and concentrated in the mammary gland [29–31]. Breast-feeding should be interrupted for 12–24h post-injection [32, 33] until the radiation dose to the child will be <1mSv. The total fractional activity ingested by the baby from in vivo-labelled RBCs is estimated to be three to five times higher than the activity in milk from in vitro labelling.

### $^{99m}$Tc-labelled human serum albumin

$^{99m}$Tc-HSA may be used as an alternative to radiolabelled RBCs. HSA was labelled with $^{99m}$Tc as early as 1966 [34]. $^{99m}$Tc-HSA is prepared from radiopharmaceutical kits containing stannous ion as the reducing agent for $^{99m}$Tc [35, 36]. However, albumin escapes from the intravascular space, and the $^{99m}$Tc-binding is not very stable; therefore, $^{99m}$Tc-HSA is inferior to $^{99m}$Tc-labelled RBCs as a blood pool imaging agent and should not be used for volume determination or LVEF monitoring over hours.

*Administered activity* The usual administered activity is 800MBq (range of 370–925MBq) for an adult patient [22]. The activity for children may be adjusted according to body weight, with a minimum activity of 80MBq to obtain images of sufficient quality [23].

*Drug interactions and side effects* No interactions of drugs or other forms of interaction with $^{99m}$Tc-HSA have been reported. After injection of $^{99m}$Tc-HSA, very few and very mild adverse effects have been observed [37].

*Radiation dosimetry* The radiation-absorbed doses to various organs after administration of $^{99m}$Tc-HSA are found in ICRP 80 [28]. The effective dose after administration of 800MBq is 4.9mSv. The typical radiation-absorbed doses for an adult to the critical organs (adrenals, heart, kidneys, liver and spleen) are 7, 16, 6, 6 and 11mGy, respectively.

*Pregnancy* A relative contraindication. Evaluation by other techniques such as echocardiography or MRI is preferred.

*Breastfeeding* There are no recommendations for cessation of breastfeeding after administration of $^{99m}$Tc-HSA [32]. However, as it is known that free pertechnetate does occur with $^{99m}$Tc-HSA, in vitro labelled RBCs should be preferred.

### Other radiopharmaceuticals

For ERNV-labelled erythrocytes, HSA are used, but for first-pass radionuclide ventriculography (FPRNV), many radiopharmaceuticals can be used including pertechnetate or $^{99m}$Tc-labelled diethylene triamine pentaacetic acid (DTPA), sulphur colloid, sestamibi and tetrofosmin. $^{201}$Tl-thallous chloride can be used in combination with MPS but is less well suited. For PET, $^{13}$N-ammonia, $^{18}$F-FDG and $^{82}$Rb may be used also for evaluation of systolic cardiac function. For a discussion of tracers for perfusion imaging with SPECT and PET, the reader is referred to the EANM/ESC procedural guidelines for MPS [15].

### Summary

In vivo and in vitro $^{99m}$Tc-labelled erythrocytes, as well as HSA, may be used for EF determination by ERNV, whereas for the FP technique, almost any $^{99m}$Tc-labelled tracer may be used. For volume determination by ERNV, in vitro-labelled red cells are preferable. The administered activity is usually 500–1,000MBq for adult patients. Pregnancy is a relative contraindication. During lactation, only in vitro-labelled red cells should be used. LVEF can also be measured by gated MPS or PET.

## 3. Acquisition of radionuclide ventriculography and gated perfusion imaging

### Introduction

Functional, radionuclide cardiac studies include several techniques:

1. FPRNV also named FP radionuclide angiography
2. ERNV, also named equilibrium radionuclide angiography, multiple-gated acquisition scan or equilibrium blood pool imaging
   - 1.1. Planar ERNV
   - 1.2. Tomographic ERNV
3. Gated myocardial perfusion scintigraphy (MPS), also named gated myocardial perfusion imaging (MPI) or gated myocardial perfusion SPECT
4. Gated cardiac PET including gated perfusion and FDG metabolic imaging
5. Non-imaging techniques

ECG gating with R-wave triggering is a key point in all those methods (with the exception of FP studies, which can be acquired as a non-gated study).

## First-pass radionuclide ventriculography

FP radionuclide ventriculography study comprises a short sequence of cardiac cycles acquired during the transit of a bolus through the heart. It provides high target to background ratio with temporal separation of the RV and LV, but imaging is possible in only one projection. The quality of FPRNV may be affected by many factors, regarding data acquisition, as well as processing parameters.

Like other modalities addressing ventricular function, FPRNV requires that the cardiac rhythm remains stable during acquisition.

*Radiopharmaceuticals* FPRNV is achievable with many compounds that do not undergo substantial first-pass pulmonary uptake. Otherwise, only the RV can be assessed. If a series of studies is required (stress/rest for example), the tracer must be rapidly cleared from the blood pool ($^{99m}$Tc-DTPA or -sulphur colloid). FPRNV can be performed just before ERNV; acquisition is then performed during tracer injection ($^{99m}$Tc-pertechnetate, labelled red cells or labelled HSA, cf. Section 2 on radiopharmaceuticals). FPRNV is also achievable with myocardial perfusion tracers such as $^{99m}$Tc-sestamibi or $^{99m}$Tc-tetrofosmin.

### *Image acquisition*

Injection technique. The radionuclide bolus should be injected rapidly using a large-gauge cannula in a proximal vein (usually antecubital). A medial vein in the right arm is preferred because venous return has the shortest and least tortuous course to the right atrium, and the arm may be abducted to straighten the veins [38]. Injection into a central venous catheter should be avoided for RVEF determination, as the bolus passage through the RV will then often include less than four heartbeats. For LV evaluation, a central venous catheter is well suited for tracer administration. FPRNV requires a minimum activity amount of 700MBq, and the bolus must be highly concentrated (<1ml) and rapidly flushed by at least 10ml saline.

*Collimator* A FP study requires a high-count rate. Some prefer a high-sensitivity, parallel-hole collimator for FPRNV studies, especially for LV studies [39, 40], whereas others prefer, especially for RV studies, a general purpose or even a high resolution, parallel-hole collimator to more accurately define the cardiac chambers and the valve planes, moving during the cardiac cycle [41].

*Field-of-view and projections* Immediately before camera positioning, a small part of the activity amount can be injected for correct positioning or a transmission can be used to aid this process. Data acquisition is started just before bolus injection and stopped after the transit of the bolus through the heart. The matrix size should be 32 × 32 or 64 × 64pixels.

In the left anterior oblique (LAO) projection used for ERNV, there is a significant overlap of the RV by the right atrium, and therefore, FPRNV is considered superior for RV EF calculation.

Optimal separation of the right atrium and RV is achieved with the right anterior oblique (RAO) projection, but the anterior projection may be preferred for assessing both LV and RV function.

Acquisition protocol. FPRNV studies can be acquired either in frame mode (with a frame time around 25–50ms) or in list mode with post-acquisition reformatting. In list mode, all detected counts are stored consecutively (with or without ECG gating), cf. Section 9 on "Physics and Software". When ECG gating is performed, the quality of the ECG signal should be checked to avoid the inclusion of artefacts. A gated acquisition allows for the superimposition of several sequential cycles and, thus, increases data density. This superimposition may lead to a loss of temporal resolution in frame mode, which can be obviated in list mode.

*Quality control* The quality of the bolus is crucial: The time–activity curve (TAC) must be checked by drawing a region of interest (ROI) over the superior vena cava; the passage of the bolus should last 2–3s for a RV study, less for an LV study [42]. A delayed or split bolus may preclude accurate data processing. If the bolus is unsatisfactory, the study should not be further analysed. The end-diastolic frame of the representative cycle should have more than 2,500 counts in the ventricular ROI [42]. A cine display of the tracer transit should be examined for visual inspection of the TAC of the RV and LV. To check patient motion, during an exercise study, an external point source may be used to aid in the registration of successive images.

## Planar equilibrium radionuclide ventriculography

*Image acquisition* Acquisition is performed with a gamma camera interfaced to a dedicated computer. Images may be acquired with either a low-energy general-purpose or high-resolution, parallel-hole collimator. Acquisition is usually

performed in frame mode, but list mode, once popular, has some advantages, cf. Section 9.

*Acquisition parameters* A minimum of 16 frames/R–R interval are required for an accurate measurement of EF, and R–R interval tolerance window should be set to 10–20% (cf. Table 3). A higher framing rate (32–64 frames/R–R) is preferred for the measurement of diastolic functional parameters (see Section 8). It is generally recommended that the heart occupies ~50% of the usable field-of-view. Typical acquisitions should last for 10–15min. Supine imaging is performed in the LAO view at 30–45° ("best septal" for RV–LV separation). The angle often needs to be altered in patients with congenital heart disease or right-sided overload. A caudal–cephalic tilting may help in separating the LV from the left atrium. Other views (Fig. 6, cf. Section 11 on "Report: display") may be relevant for assessing regional LV function: anterior view (0 or 45° less than "best septal" view), a lateral view (left cross-table lateral or 45° greater than "best septal" view, or in the right-side down left lateral decubitus position).

## Stress studies

Exercise ERNV allows LVEF to be measured both rather accurately and reproducibly *during* exercise, for comparison with the rest [43]. It may be performed in the assessment of CAD, myocardial disease or valvular heart disease. The radioactive amount injected is similar to the amount used in a resting ERNV study, although a larger activity amount may be given to shorten acquisition times during exercise.

Systolic function may also be evaluated *after* stress with stress MPS, cf. below, giving important prognostic information.

*Stress types* Different kinds of stress during imaging have been used:

- *Supine ergometer* exercise is the most convenient form of stress, with the patient's upper part of the body stabilised with shoulder restraints and hand-grips to minimise movement, but this position is not always well tolerated for a longer duration. ECG and blood pressure are monitored as for any exercise test. Exercise usually commences at a workload of 25W, increasing by 25W every 2–3min until the patient reaches one of the standard exercise test end points. Stationary bicycles are the standard means for exerting physical exercise for nuclear imaging owing to the limited motion of the chest during exercise [43].
- *Upright ergometer* exercise has been used in exercise ERNV, but patient motion is very often a problem.
- *Pharmacological stress* with a vasodilator or inotropic drug has been used in patients unable to exercise but is a rather poor substitute, and the test is best abandoned [44, 45].
- *Immediate post-treadmill/post-ergometer* imaging compared to rest imaging may give important information about possible stunning. However, it does not necessarily disclose LV systolic failure during stress, as LVEF tends to rebound back to or even above resting levels on cessation of exercise [46].

**Table 3** Scintillation camera components in relation to imaging techniques

| | FP RNV | ERNV | | MPS |
|---|---|---|---|---|
| | | Planar | SPECT | |
| Crystal | Multi-crystal, single-crystal | Single crystal | Single crystal | Single crystal |
| Heads | 1 | 1 | 2 or 3 | 2 or 3 |
| Collimator | LEGP or LEHS | LEGP/ LEHR | LEHR/ LEGP | LEHR/LEGP for $^{99m}$TcLEGP for $^{201}$Tl |
| High count-rate capability | >150,000/s | Not required | Not required | Not required |
| Gates/cycle used for evaluation of systolic function | 16–32 | ≥16 | ≥16 | ≥8 |
| Typical matrix size | 32×32 or 64×64 | 64×64 | 64×64 | 64×64 |

Scintillation cameras: General recommendations for the different imaging techniques. For the explanation of the abbreviations, see abbreviation list (before Section 1).

## Tomographic equilibrium radionuclide ventriculography

The use of ECG-gated blood pool SPECT has recently gained some popularity. In theory, the technique should overcome the difficulties of planar RNV in the separation of cardiac chambers because a complete tomographic data set is acquired. Furthermore, it allows for simultaneous evaluation RV and LV function and LV volumes without any geometrical assumptions. Currently used acquisition protocols are largely identical or strongly inspired by protocols used for myocardial perfusion SPECT.

*Image acquisition* Tomographic RNV is most commonly acquired with a two-headed gamma camera, collimator, energy window, orbit, matrix size and zoom similar to myocardial perfusion SPECT [15]. There are, however, some differences: Gating and R–R interval tolerance window should be set to 10–20%, similar to planar ERNV. Sixteen frames/cycle are preferred to eight frames, which may lead to overestimation of end-systolic counts and, hence, underestimation of the EF values.

## Gated myocardial perfusion SPECT and gated PET

The acquisition and reconstruction technique of gated myocardial perfusion SPECT is described in detail in other guidelines [15]. In Section 9, a few topics are discussed more in detail: Frame numbers, including a summed, "ungated image", and reconstruction of gated perfusion studies. Systolic function at rest is evaluated from a rest MPS. In stress MPS, cardiac function is studied after stress, which most often reflects the LV in "true rest". However, in severe cardiac failure or severe myocardial ischaemia, it may represent some degree of stunning, which has important prognostic information.

## Radionuclide ventriculography with non-imaging systems

After $^{99m}$Tc-labelling of the blood pool, LVEF can be continuously monitored for several hours with non-imaging, commercially available, radiation detectors or probes. For instrumentation characteristics, see Section 9 on "Physics and Software".

*Data registration*

At the conclusion of planar ERNV, five electrodes with respective leads are placed on the patient's chest (care should be taken that the VEST garment does not impact electrodes). It is important to confirm that the VEST is firmly placed on the patient, as movement of the main detector may cause serious errors in LVEF. The VEST garment is usually tightened down using straps and lashings. Studies in female patients should be registered without wearing a bra. The correct placement of the main detector to cover only the centre of the LV cavity is assessed under gamma camera control, placing a leaded target into the detector mount. The target should be completely flat against the collimator face and, if necessary, adjusted by moving it. It is important that the patient is comfortable to reduce the risk of motion artefacts. A second background detector is fixed at the right side of the VEST garment.

*Quality control*

At the end of recording, evaluation for technical adequacy is performed:

- Main detector position over the LV is assured by repeating a gamma camera static image with the target mounted again into the detector mount. Because of the relatively iso-sensitive field-of-view of the detector, movement of ≤1.2cm can be accepted [47].
- Beats should be rejected when varying by >20% of the average of the previous four cardiac cycles.
- Detector motion can also be identified by abrupt changes in TACs of LV and background counts.
- The study is usually considered technically adequate if the decay-corrected curve has <10% deviation from a straight line [48].

## Summary

For RVEF measurement, FPRNV is optimal, whereas ERNV cannot be used. FPRNV is technically more demanding than planar ERNV, which is the preferred acquisition mode for LVEF measurement. FPRNV is best performed in RAO projection, usually as a dynamic study and, preferably, with R-wave triggering. For LVEF measurement, planar ERNV is acquired in the LAO projection with "best septal separation" of the two ventricles and ECG triggering with at least 16 frames per cycle. Other projections for evaluation of regional left ventricular function are optional in planar ERNV. Tomographic ERNV is theoretically superior to planar ERNV but less validated, and its clinical application is not yet settled.

Planar stress ERNV performed with best septal separation view requires a stable patient position and sufficient counts for each stress level. Higher activity amounts than injected for resting ERNV may be needed.

Gated myocardial perfusion SPECT is now very widely used for comparison between post-stress and resting systolic function and for relative LV volume determination. A fixed number of accepted beats is important for good functional imaging during MPS. The LVEF and volume

determination is fairly accurate and reproducible. The low-frame number/cycle, often applied in MPS, may lead to slight underestimation of LVEF (cf. Fig. 3 in Section 5) and excludes diastolic evaluation.

Non-imaging systems can be used for LV ambulatory, systolic and functional monitoring over hours.

## 4. Right ventricular ejection fraction

### Introduction

RVEF has been examined with FP technique, with planar ERNV and with tomographic ERNV. Perfusion imaging can, generally, not be used.

### First-pass study

#### *Processing*

RVEF is processed according to TAC, usually as a reframed dataset, with frame time of 25–50ms. The ROI over the RV at end-diastole is defined from the frames coincident with the R-wave of the ECG or from the peaks of the TAC. The ROI at end-systole is defined from the frames with lowest count rates in the TAC. These two ROIs are the basis for RVEF calculation. Background subtraction is not necessary [41].

It is often a challenge to include sufficient beats for the analysis, as a rapid bolus passage through the ventricle may critically reduce the counts accumulated in the RV ROI for an accurate determination of RVEF. The later ascending and early descending parts of the TAC from the RV ROI should be used. The first part of the ascending curve and the later part of the descending curve with significant activity present in the lungs should be avoided [42].

Phase and amplitude images are of limited value but may assist in the definition of the pulmonary valve plane. The tricuspid valve plane moves significantly during RV contraction and has to be defined separately in the end-diastolic and end-systolic images [41].

#### *Interpretation*

In addition, visual evaluation of a cine loop of the bolus passage and the phase and amplitude images may assist in the

- Assessment of chamber sizes
- Detection of possible tricuspid regurgitation
- Detection of possible intracardiac shunts.

*Quality control* The transit of the tracer through cardiac chambers should be visually assessed as an endless loop format. Evaluation is often hampered by limited number of counts, limited spatial resolution and, usually, only one projection (unless a two-headed camera is used).

### Equilibrium radionuclide ventriculography

This technique has been used in several studies. However, the overlap between RV and the right atrium, which cannot be avoided during imaging, makes the method less accurate and can, therefore, not be recommended. RVEF values obtained by ERNV and FP RNV do not differ in reference populations (cf. Section 10 on “Reference values”).

### Tomographic radionuclide ventriculography

As RVEF is of importance but cannot be reliably evaluated by planar ERNV, tomography is especially interesting for the evaluation of RV function. Reconstruction and processing is usually performed with commercially available software packages. Commercially available programmes for tomographic ERNV include QBS, BPSPECT, QUBE and 4D-MSPECT. The programmes are semi-automatic or fully automatic with variable options for manual intervention. In 20–50% of the cases, automatic processing may need manual adjustments.

RVEF determination by tomographic ERNV is not so well validated with currently available software programmes. Comparison with FP RNV using QBS gave poor results in one series [49]: There was a good correlation in another one; however, 25% of patients were excluded [50]. With MRI, acceptable accuracy was obtained with QBS, but FP RNV was better [51]. In yet another study, the accuracy was good, but only few patients were included [52]. Finally, comparison with a phantom showed good correlation [53], but the value of comparison with a phantom is limited.

### Summary

RVEF is best determined by FPRNV. Quality control of bolus injection is important. Processing usually involves reframing of a dynamic study based on R-wave-triggering signals. Manual definition of RV ROIs in ED and ES is necessary, whereas background subtraction is not needed with FPRNV. Tomographic ERNV may be used as a less validated alternative, whereas planar ERNV should not be used.

## 5. Left ventricular ejection fraction

### Introduction

LVEF is by far the most important goal of all RNV techniques. Until recently, planar ERNV has been the

modality most widely evaluated. With the large body of MPS studies now performed as gated MPS, the most frequent radionuclide measurement of LVEF is performed in relation to MPS and is also well validated. FP studies and tomographic ERNV can be used but play a minor role for LVEF determination.

First-pass study

*Processing and interpretation* Background subtraction is necessary to remove scatter (spillover), approximately 20 to 30% during the LV phase [42]. Background can be identified with a ROI defined immediately outside the apical perimeter of the LV. TAC from cardiac cycles containing the maximum activity are summed in phase as for the RVEF measurement (cf. Section 4).

Planar equilibrium radionuclide ventriculography

*Processing*

Ventricular and background ROIs are created, either manually by the operator, with support of the cine loop and phase image for an accurate definition of valvular planes or automatically by the computer. Automatic programmes, provided the acquisition data are appropriate (projection separating RV from LV, counting statistics, etc., cf. sources of error below), only require a master ROI drawn by the operator over the LV, which includes the whole ventricle. Then, end diastolic (ED) and end systolic (ES) ROIs, as well as a background ROI, are defined for calculation of the LVEF and for a TAC showing emptying and filling of the LV. The efficiency of automatic methods is influenced by count statistics, target/background ratio, wall motion (WM) and pixel size. When the automatic definition fail in the accurate identification of LV contour or in the background ROI position (e.g. with the inclusion of spleen or descending activity in the aorta), it is possible in most programmes to manually modify the computer-defined ROI. Parametric images (Figs. 1 and 2), such as phase and amplitude images, may be useful for identification of the valve plane. For a better definition of cardiac contour, a temporal smoothing and, e.g. a nine-point spatial smoothing may be performed before processing. However, the TAC is computed from the original data.

From the first derivative of the TAC, additional indices of systolic function may be calculated: Peak ejection rate, the minimum value of the first derivative in the systolic interval, the corresponding time and the time-to-peak ejection rate can also be also calculated. However, no documentation is available demonstrating independent diagnostic or prognostic value.

*Visual quality control*

LVEF values provided by the automatic or manual processing should be compared with a qualitative estimate of global LV function: In case of discrepancies, reprocessing should be considered. The pattern of contraction of all left ventricular segments should be assessed using the cinematic display of each view and described using a standard scoring system (normal, mild–moderate–severe hypokinesia, akinesia and dyskinesia).

*Sources of error*

- Adequate counts/frame? Inadequate labelling (cf. section 2) with a reduced target-to-background ratio.
- Inadequate separation of the LV from other cardiac chambers (RV, left atrium); inaccurate definition of the LV ROI, either with the inclusion of non-LV regions or the exclusion of LV activity, inclusion into the background ROI of activity from spleen or descending aorta?
- Inadequate gating? An exceedingly high RR variability, e.g. atrial fibrillation, could lead to an inaccurate definition of the diastolic phase, or even to beat loss

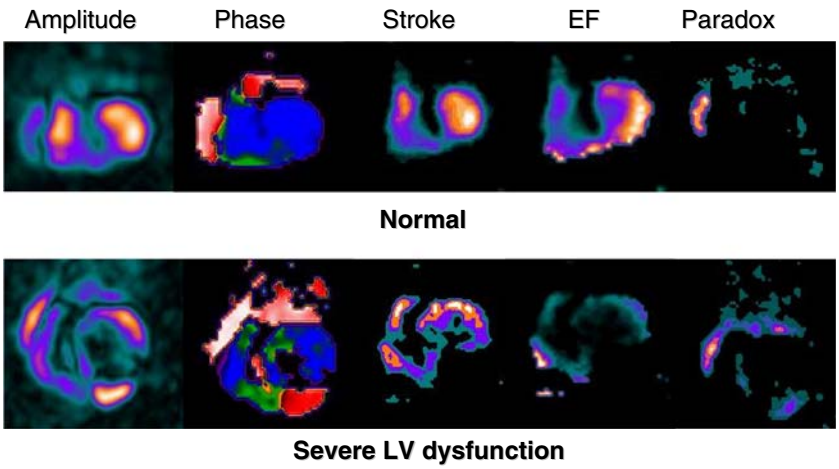


**Fig. 1** Parametric images from radionuclide ventriculographic studies obtained in a normal subject (**a**) and in a patient with severe left ventricular dysfunction (**b**)

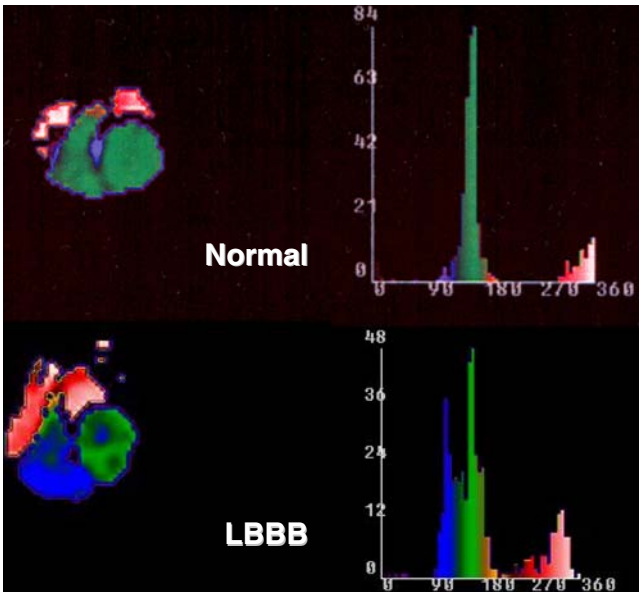


**Fig. 2** Phase image and phase distribution histogram in a normal patient (**a**) and in a patient with a left bundle branch block (*LBBB*) and normal left ventricular ejection fraction (**b**). In both patients, the standard deviations (*SD*) of ventricular phase distribution histogram were below the upper normal limits, and the homogeneous colour of the left and right ventricles also shows the absence of dyssynchronous regions. In the patient with a left bundle brunch block, the left ventricle activates after the right ventricle, as reflected by a right-to-left delay greater than 50 ms

when the RR variation is higher than the beat acceptance window.

## Tomographic equilibrium radionuclide ventriculography

The use of tomographic ERNV for LVEF is possible. However, in comparison with RVEF measurements, LVEF measurements may be more easily and as reproducibly obtained using other methods, including planar RNV. Therefore, the advantage of tomographic ERNV for LVEF lies mainly in the concomitantly acquired RV function.

The reconstruction and processing can be done using commercially available software programmes, cf. the section 4 of RV EF.

The performance of tomographic ERNV for LVEF has been analysed in several studies. Comparison of the commercially available software packages revealed acceptable agreement both among the methods and with planar ERNV [54]. In general, the values for LVEF were significantly higher than those obtained by planar ERNV [54]. Validation of (planar and tomographic) ERNV should mainly rely on comparison with MRI, considered the gold standard for LVEF, but clinically often not useful from a practical point of view. In a comparative study, the two software programmes, BPSPECT and QBS, were compared with MRI, and close agreement was found, although limits of agreement were wide [55]. Another study using MRI as reference also found good agreement with LVEF determined by tomographic ERNV [56].

In conclusion, LVEF measured with tomographic ERNV seems fairly accurate, compared with MRI as reference. However, as planar ERNV is also accurate for LVEF and much better validated, tomographic ERNV should be used with caution, and planar ERNV, presently (2007), seems preferable for clinical use.

## Myocardial perfusion SPECT and PET and FDG imaging

### *Gated myocardial perfusion SPECT*

MPS is now, in most places, performed in the gated mode. After reconstruction and reorientation of the gated SPECT projection data sets, fully automated algorithms maybe used to quantify LVEF, LV EDV and ESV. Operator-dependent quality control of automatic edge detection is obligatory, as extracardiac structures adjacent to the myocardium or nearly absent perfusion tracer uptake because of infarction can often lead to inaccurate contour findings. In these cases, the contours should be corrected. If not possible, LVEF calculation should not be done.

Many different algorithms have been developed—the most common, commercially available ones for LVEF quantification are quantitative gated SPECT (QGS) [57], 4D-MSPECT [58] and Emory Cardiac Tool Box (ECTb) [59]. A recent validation study of gated SPECT vs MRI for LVEF showed correlation coefficients of 0.85 for the ECTb, 0.87 for 4D-MSPECT and 0.89 for QGS [60]. Despite the good correlations with MRI, the gold standard for LVEF determination, the mean LVEF values differ significantly between the three algorithms, which impedes an interchangeable use. Therefore, local institution reference values should be calculated whenever possible [60]. Use of different acquisition and reconstruction parameters could strongly influence LVEF quantification [61, 62]; e.g. eight-frame data sets yield lower end diastolic volume (EDV), higher end systolic volume (ESV) and lower LVEF values as a consequence of lower temporal resolution compared to 16-frame sets (cf. Fig. 3).

### *Rest vs (post-)stress LVEF*

A normal post-stress LVEF means normal LVEF both at rest and after stress. However, post-stress LVEF might be affected by ischaemic stunning or lingering hypercontractility [63], whereas EF determined after injection at rest always represents true resting LVEF. It is now routine and recommended to perform both rest and stress studies gated, a decrease in LVEF from rest to stress, suggesting stunning as an indirect marker of severe stress-induced ischaemia.

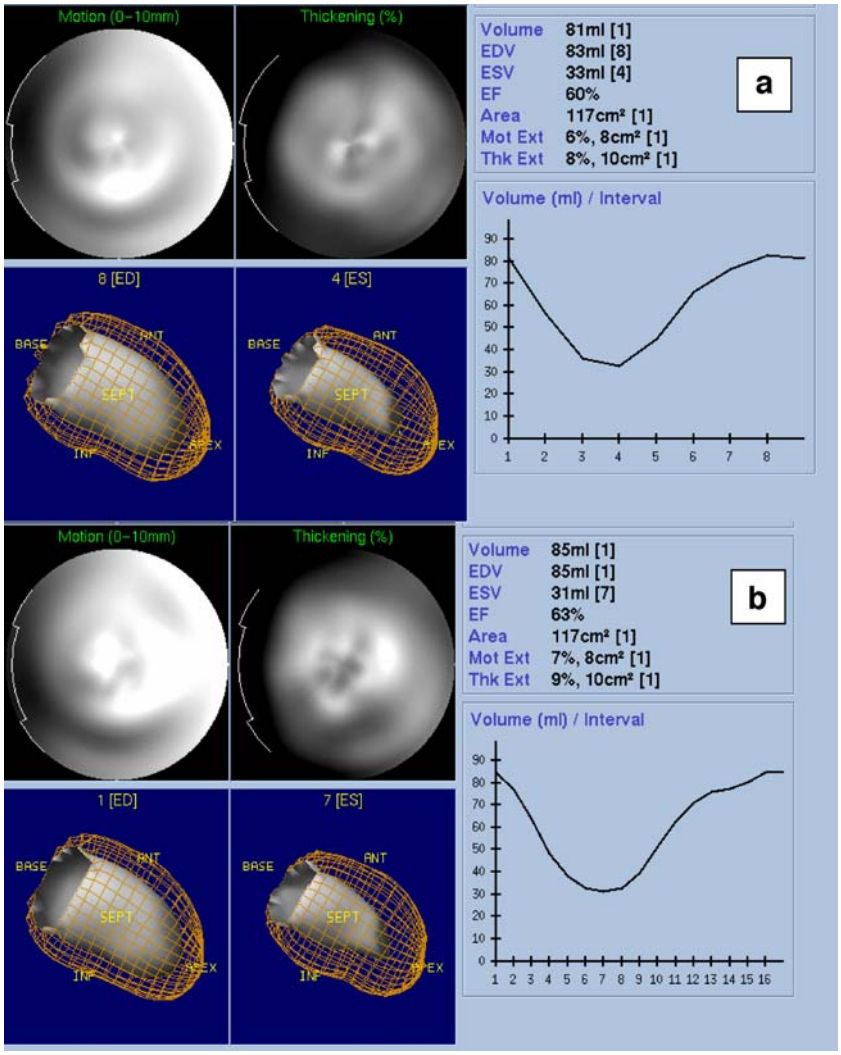


**Fig. 3** Eight-frames- (**a**), and rebinned from sixteen-frame-gated SPECT data (**b**), evaluated using QGS. The effects of the lower temporal resolution are seen in the lower end-diastolic volume (*EDV*), higher end-systolic volume (*ESV*) and reduced LVEF

It should be remembered that there is some observer variation from stress to rest also in the same patient; therefore, it is useful to determine the "intra-patient, inter-study" reproducibility of LVEF measurements in the institution to decide when a fall in LVEF from post-stress to rest LVEF is significant.

*Gated PET perfusion and metabolic imaging*

As for gated perfusion SPECT studies, commercially available software algorithms can be used to calculate LVEF from gated PET. Recent validation studies have shown the suitability of QGS and 4D-MSPECT for quantification of LVEF from gated $^{18}$F-FDG PET with similar, if not better, results ($R$ = 0.90–0.96) as for the perfusion SPECT studies [64, 65]. Also, gated PET perfusion studies can be used for accurate LVEF determination, but commercial software programmes are generally not available. If both FDG and perfusion imaging have been performed, FDG imaging is usually preferable for LVEF and volume determination. If PET–CT is performed, the modality preferred for LVEF determination may depend on local software development. It is not yet possible to give any recommendation.

Non-imaging devices

*Processing*

Radionuclide non-imaging systems do not permit absolute measurements. Estimation of LV functional parameters is based on a three-term Fourier analysis performed on each averaged time-beat period, registering changes relative to baseline. ED and ES counts are calculated as the inflection points at which the first derivative curve change sign from positive to negative and vice versa, likewise for peak ejection and filling rates [66]. Fixed background correction may be useful in stable physiologic states but is not always reliable; e.g. when LV ED pressure is changing and background count rate may increase. Thus, if monitored background registered by the detector placed over the right

lung does not change significantly during the period of evaluation, the constant EF background correction can be applied for analysis of the data throughout the period of observation. On the other hand, variable background correction should be applied when background changes are detected through its monitoring. Increased distance in certain patients (e.g. obese subjects, women with large breasts and patients with chronic obstructive pulmonary disease) between the detector and LV may lead to LVEF overestimation with fixed background correction.

*Validation and interpretation*

Accuracy and reproducibility of data have been validated in comparison with conventional gamma cameras at rest and during physical and mental stress, as well as during interventions [67–70]. The validation of LV function measurements to various different stimuli has been established, and LV function responses during normal activities of daily life have been defined [71]. Studies in patients undergoing percutaneous transluminal coronary angioplasty have been performed for clinical validation of the system [72].

Changes in LVEF should be interpreted in accordance with the type of activity being performed. Normal LVEF responses to physical exercise are uniform, showing an increase during exercise, but LVEF may decrease at peak exercise. A decrease in LVEF is often seen in ambulatory patients with known CAD during physical exercise but may be elicited in healthy subjects [73]. Heart rate and blood pressure changes should be considered when studying LVEF responses [73], especially in patients with depressed baseline systolic function [74]. The variability in LVEF measurement with the commercially available Vest at rest and exercise is £6%, a value similar to that obtained with traditional radionuclide ventriculography [47, 71, 73].

Summary

LVEF measured by planar ERNV is most often done using commercial software programmes that, after manual definition of the location of the LV, work rather automatically. With the same software system, LVEF values are reproducible with fairly low intra- and inter-observer variations, but differences in LVEF determination between different programmes may be significant. Manual modifications of the defined ROIs are occasionally necessary. LVEF measurement can also be achieved from FPRNV, sometimes useful, as well as from tomographic ERNV. The use of gated MPS is now the most frequently used radionuclide technique, giving reproducible, maybe slightly underestimated, LVEF values. Gated cardiac PET can give the same additional, valuable information on cardiac function as MPS. Finally, reliable, ambulatory monitoring of LVEF over hours can be accomplished using a non-imaging device. With all the techniques, a regular ventricular rhythm is required.

## 6. Left ventricular volumes

Introduction

The measurement of absolute left ventricular volumes (LVV) is possible both with the FPRNV and ERNV techniques, as well as with gated MPS. There is limited documentation of independent clinical value of measurement of these absolute volumes. Measurement of relative volume changes in stress–rest perfusion SPECT is simpler and may provide both pathophysiological and prognostic information. Recent work has shown the importance of measures such as post-stress LVEF and ESV, as well as "transient ischaemic dilation" (TID), which can be calculated from stress and rest LVV, as prognostic indicators. A number of commercial packages are available to calculate LVVs and other functional parameters from tomographic ERNV or tomographic MPS.

Planar equilibrium radionuclide ventriculography

The measurement of LVV by planar ERNV is compromised by the difficulty in measuring a three-dimensional parameter using a two-dimensional imaging technique. A number of methods for overcoming this limitation have been proposed. Many of these require blood sampling [75] or more invasive techniques such as thermodilution [76]. Techniques have also been developed using geometrical methods. These include the use of semi-automated methods based on empirically derived threshold values [77] or theorems developed using reference volumes [78, 79]. All of these techniques measure LVEDV and calculate the LVESV from the measured LVEF. If it is necessary to use planar ERNV, the count ratio technique of Massardo et al. is recommended, as it has been shown to produce the most reproducible measurements [80].

Tomographic equilibrium radionuclide ventriculography

The acquisition of ERNV data in tomographic mode removes the limitations inherent with the planar technique. However, it introduces other errors, such as non-uniform attenuation, scatter and the partial volume effect, which must be addressed if accurate quantification is to be achieved. The numbers of comparative studies between the available techniques are very limited. These have shown the LVEF results from each software package to be reproducible but not interchangeable [54]. The results for LVV have been shown to be highly variable [54] with up

to a 100% difference between different packages. The BP–SPECT algorithm has been validated to a greater degree than the others [81, 82] but has been shown to over-estimate LVV in phantom experiments [82]. Until further studies have been carried out validating LVV calculations using a gold standard such as MRI, these results should be treated with considerable caution for use in clinical practice.

## Gated myocardial perfusion SPECT

The availability of systems capable of carrying out gated SPECT has increased greatly in recent years. The addition of functional data, such as ESV, to the perfusion information has been shown to improve risk stratification in patients with ischaemic disease [9, 83]. As for tomographic ERNV, the most complex task in quantification is the detection of the ventricular edges. In this case, both the epicardial and endocardial surfaces of the myocardium must be defined. This is complicated by the thin myocardial walls, especially at end-diastole, by the presence of perfusion defects and by areas of high uptake in adjacent organs.

A number of commercial packages are available to provide quantification of LVV from gated MPS. These include QGS [57], ECTb [59], 4D-MSPECT [58] and Myo-SPECT [84, 85]. These have taken a number of different approaches to the task of myocardial edge detection. The radial sampling of the myocardium has been carried out using spherical sampling from the ventricular centre of mass [57] or a hybrid of spherical and cylindrical sampling [59]; see also Section 9 on "Physics and software". Edges have been detected using fixed threshold levels set on asymmetric Gaussian functions [57], statistical analysis of radial count profiles [84] and relaxation labelling [86].

### *Accuracy of left ventricular volumes*

The validation of these packages has also generated a considerable amount of work in recent years. A gold-standard technique has been used with these in a number of studies [59, 87–89]. It has generally been found that LVV calculations show good agreement with techniques such as thermodilution [87] and MRI [59, 89]. However, there remain problems with the detection of ventricular edges in the presence of large perfusion defects and high extracardiac activity [88]. Comparative studies between the commercial packages have also been carried out [60]. These have shown that EDV and ESV values obtained from the packages agree well with MRI over a wide range of volumes. Algorithm-inherent errors in volume calculation unfortunately preclude interchangeable use of the packages [60]. The reliability of relative volume changes in the same patient from rest to stress is generally quite simple and has been documented to be of clinical importance as mentioned above.

### *Influence of acquisition and processing parameters*

The commercial packages will provide adequate results with $^{99m}$Tc and to some degree with $^{201}$Tl myocardial perfusion data using standard stress or rest acquisition protocols. Each package generally provides a recommended protocol for the acquisition of data. The questions of 180 versus 360$^{o}$ acquisition and 8 or 16 frames/cycle tend to be determined by practical imaging concerns. It has been shown that 16 time-bin data provides more accurate volumes [57], but the consequent increase in the counts required may sometimes result in the imaging time longer than the patient can comfortably tolerate.

Two other more subtle factors have been detected, requiring some consideration:

- The application of a Butterworth pre-filter rather than the prescribed post-filter with the QGS package has been shown to result in over-estimation of EDV and ESV [62].
- The reproducibility of volume results from QGS has been shown to be highly dependent upon the count levels in the reconstructed data [90].
- This raises potential issues for sites where limited activities are injected. A 400MBq limit (specified in the UK) was shown to be inadequate for large patients, and higher activity amounts have accordingly been recommended in the European guidelines on perfusion imaging [15].

## Summary

Ideally, planar techniques should be avoided. The choice between the tomographic techniques will depend more on departmental logistics. The MPS techniques have undergone rather rigorous assessment and are widely used compared to the ERNV methods for volume determination. In general, the MPS quantification packages produce fairly robust results and will be the optimal choice, especially for relative volume changes from rest to (post-)stress examinations. Transient ischaemic dilatation (TID) and other data show important prognostic implications [91, 92]. However, considerable work remains to be done regarding the exact limits at which clinically significant information can be derived. Therefore, unless users are prepared to generate their own normal ranges using the local equipment and patient population, these techniques should be used with caution for clinical purposes. Furthermore, exercise, dobutamine and vasodilator stresses may not be comparable.

## 7. Left ventricular regional function

### Introduction

FP and planar ERNV are limited for accurate evaluation of regional wall motion of the LV by showing only a two-dimensional image. This limitation may be overcome by tomographic techniques, but quantification algorithms are not commercially available for any of the techniques. In gated MPS, analysis of regional abnormalities has the advantage compared with RNV techniques of including both WM and wall thickening (WTh).

Regional wall motion of the RV cannot be determined by any radionuclide techniques.

### Planar radionuclide ventriculography

Assessment of the regional ventricular WM should begin with a visual qualitative assessment of the dynamic images as a cinematic loop in all three standard views. Such a review is also a quality control of the whole study.

- WM is best evaluated with linear gray scale without computer-derived edges [93].
- WM evaluation with planar imaging needs three projections (Fig. 4), yet some overlapping with other cardiac chambers is a limitation.
- Abnormalities of contraction should be described using the conventional scoring system: normal WM, hypokinesia, akinesia, and dyskinesia [94].
- If stress images are available, they should be compared with the rest images, with both cine loops shown simultaneously.
- Principal components analysis is an alternative form of assessing regional function, creating a visually more pleasing motion image by reducing the appearance of noise in the cine. However, the experience with this technique is limited; it should, therefore, only be used as a supplement to the standard cine loop assessment [95]. For a more systematic evaluation of the LV regional function, a supplemental, quantitative analysis can be performed.
- The LV can be divided into radial sectors by constructing radii from its centre, and each individual, regional sector is associated with a TAC from which EF and filling parameters can be derived.
- *Functional or parametric images* can also be generated (cf. Section 5 with Figs. 1 and 2 on LVEF and Section 9 on "Physics and software"). They are more sensitive for the detection of abnormal WM and superior to visual assessment of the raw data alone [96], and areas of dyskinesia and akinesia are clearly distinguished from normal contraction, but it may be difficult to discriminate hypokinesia from normal WM [97]. The smallest amplitude is often observed at the base and the greatest amplitude at the apex of the LV. The phase image histogram of the LV should consist of a single narrow peak, as all parts of the ventricle should contract with the same timing.

  *Phase and amplitude images* may be used to help to define regional ventricular contraction abnormalities and aneurysms caused by coronary disease, as well as other cardiac diseases. Ischaemic myocardium typically has reduced, delayed or paradoxal contraction. These regional abnormalities broaden the peak of the phase. In

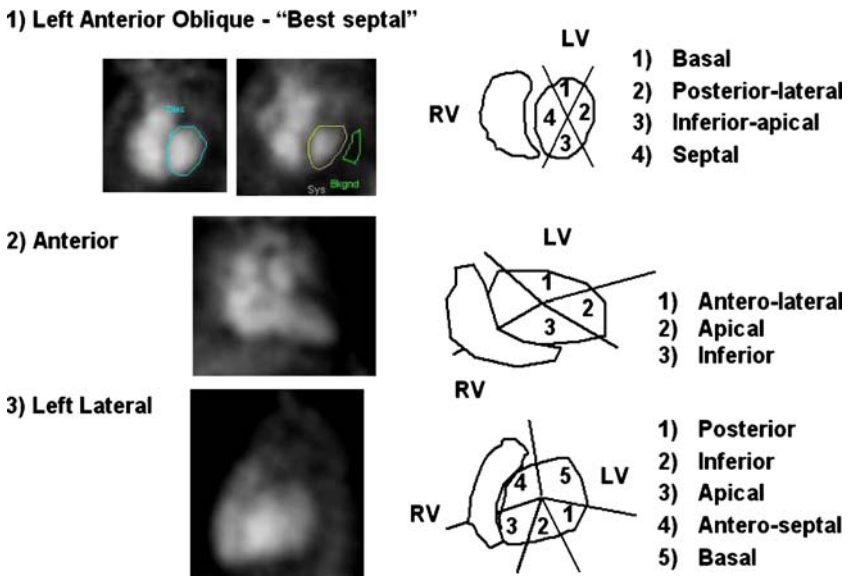


**Fig. 4** Projections and nomenclature: schematic representation of RNV projections and wall nomenclature in LAO (1), anterior (2) and left lateral projections

heart diseases characterised by diffusely impaired contraction, such as non-ischaemic cardiomyopathy or anthracycline toxicity, deterioration of contraction is usually first noted in the apex region, commonly described as an "apical lag". Additionally paradoxical, septal motion is often seen in patients with left bundle branche block (LBBB) or after open-heart surgery [98]. In general, the phase image is more sensitive for detecting abnormal function than methods looking only at the extent of contraction [99, 100].

### Tomographic radionuclide ventriculography

- Firstly, a visual assessment of the extent of regional WM should be obtained, preferably by displaying the full set of tomograms in the three standard orientations. Cinematographic loops' display of long and short axis is standard on most commercial computer systems as part of gated SPECT software packages.
- Additionally, software programmes create 3D-surface shaded displays and/or volume-rendered displays in which the end-diastolic cardiac silhouette is presented as a 'bird cage', used as a fixed reference for WM assessment (Fig. 3 in section on LVEF). These 3D images can be displayed in multiple cardinal views or the user is allowed to rotate the beating cine 3D display into any angle for best assessment of a particular cardiac region.
- Optionally, a semi-quantitative analysis of regional function can be obtained by performing regional LVEF. A polar map of regional EF can be constructed from the set of short axis tomograms in a similar way as in planar RNV, and quantitative regional EF values of all LV segments are displayed in one image.

### Gated myocardial perfusion SPECT

An increasingly popular technique for the assessment of regional function is gated MPS, which allows simultaneous assessment of myocardial perfusion and function in the same segments. An important advantage of gated MPS compared to FP and ERNV is that the former provides information not only on regional WM but additional information on WTh, which can help distinguish contraction from translation and rotation. Moreover, knowledge of regional function improves specificity and confidence in the evaluation of the perfusion data by allowing distinction between true abnormalities and attenuation artefacts. Furthermore, evaluation of regional ventricular function by gated MPS can be a valuable tool for assessment of potentially reversible systolic dysfunction and adds prognostic information above that obtained from the perfusion data alone. However, it should be remembered that preserved WM/WTh in an apparent, stress-induced perfusion defect does not prove the perfusion defect to be an artefact, as the functional parameters (WM and WTh) reflect cardiac function during imaging, whereas the myocardial $^{99m}$Tc tracer uptake reflects the perfusion just after tracer injection.

1. A visual qualitative assessment of the regional ventricular WM is made by displaying the dynamic images as a cinematic loop in all three standard views. Such a review is also a quality control of the whole study.
2. WM should best be evaluated in grey scale without computer-derived edges using the conventional scoring system (normal WM, hypokinesia, akinesia and dyskinesia). Computer-generated contours can be helpful, but they should not be used as sole determinant of WM [93].
3. If stress images are available, they should be compared with the rest of the images, with both cine loops shown simultaneously.
4. WTh is related to the increase in counts from diastole to systole and is best evaluated in a continuous colour scale without computer-derived edges. As with the WM, computer-generated contours can be helpful but should not be used as sole determinant of WTh.
5. It is commonly accepted that WM and WTh may be incorporated into a single qualification while noting the discordance between motion and thickening when it occurs. WM and thickening are generally concordant. The main exceptions include [101]
    1.1. Previous coronary bypass surgery.
    1.2. RV overload. WM in the septum is decreased, whereas WTh is preserved.
    1.3. LBBB.
    1.4. In the presence of large infarcts, reduced or absent motion but normal thickening can be observed in adjacent, peri-infarct regions.
    1.5. Preserved WM but reduced WTh can occur in an abnormally perfused segment as a result of passive inward motion of non-viable myocardium (tethering) secondary to hypercontractility of adjacent non-infarcted segments.

At the time of writing (2007), programmes that quantify WM parameters in gated MPS have not been proven to be more precise than conventional, visual analysis and cannot be recommended for use in clinical practice.

### Summary

In addition to global LV function, planar ERNV can be a useful tool for the assessment of regional ventricular

function but is limited by the 2D mode. Tomographic ERNV circumvents this limitation, but documentation of the additional benefit compared to planar ERNV is not yet available. Gated MPS is an obvious way of assessing regional LV function along with perfusion within a single study. Compared with perfusion data alone, it offers additional, clinically valuable, diagnostic and prognostic information with enhanced confidence in the interpretation of MPS data. Software for absolute quantification, although desirable, is not yet commercially available.

## 8. Left ventricular diastolic function

### Introduction

Patients with heart failure and preserved LV systolic function may have significant abnormalities in diastolic function, a condition called diastolic heart failure, which include (1) signs or symptoms of congestive heart failure, (2) normal or mildly abnormal systolic LV function and (3) evidence of diastolic LV dysfunction [102]. It is reported to be particularly frequent in elderly, hypertensive and/or diabetic patients with chronic heart failure, as well as in hypertrophic cardiomyopathy. The definition and clinical value of the diagnosis of diastolic failure are debated in the literature. Planar ERNV is the only radionuclide technique, which has been validated for the assessment of diastolic function. Evaluation of diastolic function with tomography should not be undertaken, as the frame rate in SPECT imaging is usually too low (<32 frames/cycle).

### Quality control

A critical determinant of the quality of the images for LV diastolic function evaluation is the count statistics of the ERNV images (in each frame and in the entire study). To describe LV diastolic filling accurately, a more complete assessment of the TAC is required than is used for LVEF determination. Thus, variability in the heart rate and, subsequently, in diastolic time, makes it difficult to record events in late diastole. Assessment of the adequacy of the R-wave trigger before the acquisition should be performed, including visualisation of the beating heart. Backward gating, if available, rather than forward gating is to be preferred for evaluation of diastolic function, cf. Section 9 on "Physics and software". The parameters to be controlled are summarised below:

- Frame rate of <30ms frame duration or ≥32 frames/cycle.
- R–R interval tolerance of ±10%.
- Per cent accepted beats of >90%.
- After acquisition, drop-off in the end of cine loop should be minimal.
- Well-defined systolic trough.
- End-diastole: cps at the beginning of TAC = cps at end of TAC.

### Parameters measured and image analysis

The radionuclide measurement of diastolic filling is derived from the LV TAC, which closely approximates LV cavity volume as it varies throughout the cardiac cycle. Diastolic filling parameters derived by ERNV include [95, 103, 104]

- *PFR* Peak filling rate, i.e. greatest filling rate in early diastole
- $PFR_{SV}$ PFR normalised to stroke volume
- *TPFR* Time-to-peak filling rate

### Interpretation

Diastole can be divided into four phases: isovolumic relaxation, rapid early mitral inflow, diastasis and atrial systole. The interpretation of the diastolic filling portion of the LV TAC depends on both qualitative and quantitative assessment of the TAC. Qualitative analysis of the shape of the curve is frequently sufficient to detect gross abnormalities of diastolic filling, as quantitative results vary considerably from laboratory to laboratory [105]. An increase in the atrial contribution to filling associated with a variable decrease in the early PFR is typical of both normal aging and hypertension [106]. Prolongation of isovolumic relaxation is typical of hypertrophic cardiomyopathy, and delayed and decreased rapid filling is typical of CAD [107].

### Summary

Planar ERNV is the only validated radionuclide imaging technique for evaluation of diastolic function. It is important to use high amounts of activity, a frame duration of ≤30ms and low R–R interval tolerance, and still get a high number of accepted beats. Diastolic function may be expressed as PFR, $PFR_{SV}$ or TPFR. Documentation of the clinical value of diastolic function in addition to the parameters obtained for systolic function is limited.

## 9. Physics and software

### Introduction

Nuclear cardiology functional studies are performed using

- Scintillation cameras (single and multicrystal cameras)
- PET scanners

- CT scanners (low-dose and multislice (4, 8, 16, 32, 64 and 256 slice scanners) in combination with SPECT and PET
- Non-imaging systems

This section will discuss certain hardware and software aspects of the use of scintillation cameras and non-imaging devices related to functional cardiac evaluation, whereas the hardware and software of PET and CT scanners are beyond the scope of this section.

## Scintillation cameras and collimators

*Gamma camera types* Different kinds of scintillation cameras can be used for functional nuclear imaging. The cameras may accommodate a different set of performance parameters for the different imaging techniques (Table 3).

For FP studies, it is paramount to obtain a sufficient count rate (>150,000 accepted cps) for adequate quantification of the heart function. This requires a camera system capable of processing such a high count rate, much higher than needed for equilibrium RNV or gated MPS.

*Detectors and rotation during SPECT* A single head camera is adequate for FP and planar ERNV imaging. For tomographic functional imaging, usually a two- or three-head camera is needed to limit total acquisition time and, by this, avoid patient motion during acquisition. With a dual-head system, normally, either a fixed 90° head configuration or a variable head configuration set to 90° is used to allow for tomographic 180° imaging. Projections may be acquired from a semi-circle with only a 90° rotation of the dual-head configuration, resulting in an increasing imaging speed.

*Crystals* Most cameras use a NaI (Tl) crystal design with 3/8-in. crystal thickness. Multicrystal NaI (Tl) cameras were built for high count-rate first-pass imaging. Scintillation cameras doubling as coincidence cameras for positron emission imaging usually utilise thicker crystals (up to 1in.) to accommodate for 511 keV photons in addition to the lower energy $^{201}$Tl or $^{99m}$Tc photons.

All crystal designs are capable of producing good quality images suitable for analysis of LV function.

*Collimators* Most often, parallel-hole collimators are used for cardiac imaging. For this collimator type, holes are oriented perpendicularly to the detector head without any tilt with respect to the detector surface and without any variation over the surface area. The most commonly used collimator is the low-energy, general purpose (LEGP) type (also named low-energy, all-purpose, LEAP). Other collimator types (low-energy, high-sensitivity, LEHS; low-energy, high-resolution, LEHR; converging, diverging and pinhole collimators) have their advantages and disadvantages, and may be preferred for certain examinations. The parallel slant hole collimator [108, 109], with holes having a caudal tilt, enables imaging of the heart from an oblique angle in the cranio-caudal direction. This allows for better separation of the LV from the left atrium. No clinical data are available that shows whether this translates into a more accurate quantification of left-ventricular function with ERNV; therefore, this collimator has not attained widespread clinical use.

## Study acquisition parameters

### *Frame mode and list mode*

Nearly all equilibrium studies are acquired in a frame-based mode where the operator specifies the acquisition parameters *before* the actual scan. In a list mode acquisition, the detected events are stored individually with information about time and position on the detector, and potentially, also the energy of the event intact. This retains all information of the scan and leaves a maximal freedom for the subsequent analysis in that frame definition can be performed *after* the scan. List mode acquisitions were popular in the 1980s but have a disadvantage in the very large amount of data produced with subsequently more expensive storage requirements. This problem has disappeared with the fast progression of computer technology. So far (2007), list mode acquisition has, however, not yet again seen widespread implementation.

### *Rotation orbit in tomography*

Projection data acquired from a full 360° orbit or from a reduced 180° orbit can be used for SPECT imaging of the heart. The 180° orbit is chosen to range from the right anterior oblique (RAO) to the left posterior oblique (LPO) positions because, here, the heart is relatively close to the detector and the photon attenuation is reduced as compared to the right lateral and posterior positions. For a two-headed camera in a 90° configuration, the detector setup has to rotate only 90° to cover a 180° orbit, thus, reducing acquisition time. For a three-head camera with an angle of 120° between each pair of heads, a complete 360° orbit is covered by rotation of only 120°.

Image acquisition with a 180° orbit may lead to increased image inhomogeinity when compared to acquisition with a full 360° orbit [110]. Likewise, the use of an elliptical or body-countour orbit may lead to a small difference in image quality compared to a circular orbit, as the resolution of projection images used for reconstruction differ, dependent on the detector–heart distance. This is

counterbalance by less imaging time (less risk of patient motion) and better sensitivity, respectively, associated with these orbit definitions. No consensus has been reached as to the preferred orbit, and each choice is deemed appropriate. No important differences in quality have been demonstrated for operation in step-and-shoot mode vs continuous motion rotation of the camera heads.

*Equilibrium radionuclide ventriculography during exercise*

Planar ERNV can also be performed during exercise. As a maximum level of exercise cannot be maintained for long, tomographic ERNV is not suited for exercise imaging. (tomographic stress MPS does not show cardiac function *during* but *after* the stress test, cf. Section 3 on "Acquisition of radionuclide ventriculagraphy"). Stationary bicycles are the standard tool for exerting physical exercise for nuclear imaging, owing to the limited motion of the chest during bicycle exercise [43]. Exercise in a supine position is not always well tolerated for a longer duration so that exercise in an upright or semi-upright position is often advantageous, if not precluded by camera design. Nevertheless, the number of acquired counts during the state of maximal exercise is often limited, and motion can occur, giving less exact quantification of LVEF compared to rest imaging. Treadmill exercise cannot be recommended for ERNV because of motion artefacts. Treadmill exercise may be adequate for first-pass imaging in many cases, provided that motion compensation schemes are employed (e.g. by using a fiducial marker attached to the patient's chest) [111].

*Attenuation and scatter compensation in SPECT*

The use of attenuation compensation (often together with "scatter correction") for MPS can help to resolve ambiguities in measured regional tracer uptake (hypoperfusion vs attenuation), especially in the inferior wall. For attenuation, compensation systems used in clinical routine imaging require an auxiliary transmission scan with a radiation source of known activity outside of the patient, either by an external rod or flood source filled with a photon-emitting isotope [112–114] or an X-ray tube with an opposing detector that form a CT system [115, 116]. CT-derived attenuation maps are less noisy than those derived from an external radiation source; however, spatial and temporal coregistration may be less than ideal because of respiratory, cardiac and patient movement. Whereas a slow CT scan with a scan duration long enough to provide a good average of respiratory and cardiac motion is acceptable for cardiac SPECT studies, fast CT under breath-holding conditions can lead to serious quantification artifacts and cannot be recommended without adequate compensation schemes (not commercially available at the time of writing). All implementations of SPECT attenuation compensation are elaborate and can lead to new inaccuracies. Therefore, both compensated and non-compensated images should be evaluated for clinical perfusion studies. However, the impact of attenuation-scatter compensation on the quantification of left-ventricular function is limited. If in doubt, the non-compensated images can always be used for functional analysis and compared to normal values obtained in this way. All, commercially available, software programmes use non-corrected images. It is generally recognised that attenuation compensation should be accompanied by scatter compensation [15]. In recent systems, the implementation of compensation for collimator response function may improve spatial resolution and make the determination of ventricle surfaces more accurate because of the smoothing effect of the method.

*Cardiac gating*

*Radionuclide ventriculography* With the notable exception of first-pass imaging [117] that can be performed with, as well as without, gating, all other imaging techniques make use of cardiac gating based on R-wave triggering of the ECG. It should be remembered that the relationship between electric excitation and heart contraction may be abnormal (e.g. left-bundle branch block). Data are summarised in Table 4.

*R–R interval tolerance and beat rejection* The range of accepted cycle lengths has to be defined to exclude data from non-representative heart beats, e.g. from extrasystoles. Also post-beat rejection can be done, as the ejection fraction from the contraction after an extrasystole can be non-representative. A range of the commonly used 20% means that all heart cycles with a cycle length within a 90–110% interval of the

**Table 4** Gating

| Parameter | Comments |
|---|---|
| Electro-mechanical dissociation | Diastole: bundle branch block<br>Systole: not defined from ECG |
| Forward gating | Best for systolic evaluation |
| Backward gating | Best for diastolic evaluation |
| Number of frames/ cycle | RNV: ≥16 frames for ejection fraction<br>RNV: ≥32 frames for diastolic function<br>MPS: ≥8 frames is acceptable, but LVEF slightly underestimated if <16 frames |
| R-R interval tolerance | RNV: standard, ±10% of average interval, may be increased with arrhythmias<br>MPS: standard, ±30% of average interval, may be increased with arrythmias |
| List mode | MPS: If available, it may solve many problems outlined above, but processing is more time consuming |

Different methods of cardiac gating for different purposes

average heart rate are accepted, allowing for the physiologic variations of heart cycle duration.

Cardiac gating in ERNV is performed in three different ways:

- Forward gating. The R wave is the starting signal, all counts being registered thereafter and distributed into gating intervals predefined from the mean heart cycle length divided by the number of gates. The first gates (systole) are relatively exact; the later gates (diastole) less exact owing to changing cycle length.
- Backward gating. The R-wave from the following heart cycle is the reference point, counts being distributed into the gating intervals going backwards in time. With backward gating, the gating intervals during diastole are more exact and less exact during systole.
- Variable timing. With the "variable timing", the interval length can be calculated individually for every heart cycle. This gating scheme allows for better timing of both early and late gates but is rarely accessible in commercial systems.
- Acquisition in list mode is rarely possible but optimal, as it not only allows for the generation of a non-gated frame from all recorded events but also for an acceptance window tailored to the particular patient and the particular acquisition *after* the scan.

*Myocardial perfusion scintigraphy* The synchronised acquisition of SPECT data is usually obtained with 8 or 16 frames (cf. [15]). Although the EF is underestimated when using 8 frames as compared to a 16-frame acquisition (Fig. 3), the deviation is small (low single-digit EF points) and consistent, so that 8-frame acquisition is considered adequate when reference values are chosen accordingly. In some cameras, the discarded counts are collected in a separate frame so that a non-gated frame can be generated from all detected events irrespective of gating. If not available in the system, these 8 or 16 sets of projection images are summed to obtain a single "ungated" projection set. Thus, when using a summed-up projection set from patients with severe arrhythmias, the perfusion information can be based on a data set with reduced counts in some steps of the rotation. Hence, a "time per projection" mode should only be used when the camera system stores all data for perfusion processing. Otherwise, a fixed number of accepted cardiac cycles per projection must be acquired.

## Image analysis parameters

A large number of computer programmes have been developed for analysis of cardiac function in nuclear cardiology, ranging from simple programmes for image presentation in cine mode and simple tools for ROI analysis to sophisticated programmes offering an almost automatic, operator-independent, quantitative assessment of functional parameters. Algorithms for quantification of parameters are generally based on changes during the cardiac cycle in counts or in geometry. The operator is left with the task of quality control, occasional manual interaction and final interpretation of the results.

## Image presentation

### *Cardiac chambers*

*Planar imaging* The acquired image frames can be displayed in cine-mode on the computer screen or as a time series of images on paper or film. A linear grey scale map is often adequate for image presentation, but a color map may be useful, especially for phase and amplitude images.

*Tomographic imaging* The software offers the possibility to display the projection data, usually in a cinematographic way. These images are inspected mainly for the purpose of quality control to exclude patient movement during the scan, as well as other imaging errors. For further analysis, tomographic images are derived from the projection data by reconstruction. Several orientations are used.

The primarily reconstructed images are the so-called

- Transaxial images orientated perpendicularly to the long axis of the camera. They reflect the orientation of the scanner and usually of the patient.

For clinical analysis, slices are generated by means of image transformation from the transaxial slices by reangulation to present data in relation to the orientation of the LV:

- Vertical long axis slices of the LV going from the anterior to the inferior wall
- Short axis (SA) slices perpendicular to the long axis: going from the apex to the base
- Horizontal long axis slices perpendicular to the SA, going from the septal to the lateral wall

Algorithms have been developed and validated for automated, operator-independent reangulation of the LV [118, 119]. In addition to increasing the time efficiency of the analysis, it also decreases operator dependency. Software is usually also available for operator-dependent, manual reangulation. Inadequate reangulation can lead to serious artifacts.

### *Time–activity curves*

Change of activity over time within one ROI, e.g. left ventricular cavity, reveals parameters of cardiac function

both for FPRNV and planar ERNV. Analysis software regularly provides the option to specify a closed contour on one or several images enclosing the ROI. The contour can be a geometric shape, such as a rectangular box or a circle, where the operator only has to specify the centre and radius, or a free-form closed figure. Instead of using the TAC directly for analysis, often, a substitute curve is used that approximates the TAC closely. The substitute curve can be a single, analytical function for the whole TAC; it can be composed of separate functions for distinct intervals of the whole TAC or it can be locally defined on a sliding scale that takes into account the central and several neigbouring points. There is no general consensus as to what interpolation scheme is optimal.

*Parametric images*

In parametric images (Figs. 1, 2 and 3 in Section 5), each pixel is the result of a mathematical operation involving the acquired (background-corrected) image data. The parametric images used for functional nuclear cardiology are used to depict certain features within the image series that are not obvious in a cinematographic display of the original images. A variety of parameters may be used:

- Stroke volume image. Pixel-wise subtraction of ES from ED images
- Regional EF image. Pixel-wise division of stroke volume image by ED image
- Paradox image. A pixel-wise subtraction of ED from ES image with negative values then set to zero
- Phase analysis image. Regional differences are depicted in the timing relationship of contraction (asynchrony). The phase is displayed as a parametric image with pixels with low amplitude blacked out.

In normal subjects, phase values over the right and left ventricles are similar, and the ventricular phase histogram consists of a single narrow peak, with the RV mean phase occurring slightly earlier than the mean LV phase. In patients with right bundle branch block, the RV mean phase occurs after the LV one, with a delay between the ventricles generally not as large as that seen in LBBB, where the LV mean phase occurs significantly later than the RV mean phase. Myocardial ischaemia, fibrosis or conduction disturbances may broaden the phase histogram, as reflected in a higher SD, and may be implicated in delayed contraction. The atrial chambers, as expected, had a sine-like behaviour instead of the cosine-like behaviour of the ventricles, giving approximately a 180° phase difference between the atria and the ventricles (Fig. 2).

- Amplitude images can be displayed as a parametric image and offers information similar to the regional stroke volume image as defined above but with a pixel-wise instead of a global timing of ED and ES states [120, 121].

Software features of radionuclide ventriculography

*Ejection fraction*

The most important goal for functional cardiac imaging is EF measurements. EF can be calculated from the counts in ED and ES as

$$\mathrm{EF} = \frac{\mathrm{Counts_{ED}} - \mathrm{Counts_{ES}}}{\mathrm{Counts_{ED}}}$$

*First-pass radionuclide ventriculography* Software must offer cinematographic view capability, as well as ROI and TAC analysis capability. The relevant part of the TAC for RV or LV, supported by cinematographic images, is then reframed to an average cardiac cycle, covering 4–10 beats, less beats for RV than for LV. The reframing is either performed by an automatic programme based on the R-trigger signals or based on manually detected peaks in the TAC. The further analysis follows more or less the ERNV analysis, with automatic or more manual definition of the ED and ES images from the images, often presented in a cinematographic mode.

*Planar equilibrium radionuclide ventriculography* Software must offer cinematographic display of acquired images and the possibility to do ROI and TAC analysis. Software may provide semi-automatic or automatic ROI contours. The background ROI is placed near to the ventricular activity, if possible, *within* the LV cavity during *ED* but *outside* the ROI of the LV in *ES*, ES count rate in this background ROI being used for background compensation. Regional systolic and diastolic wall motion can be evaluated.

*Tomographic ERNV* A reconstruction of the SPECT projection data is necessary to obtain tomographic images. The historic standard method is the filtered back-projection, but this method is being replaced by newer and more computationally intensive iterative reconstruction methods. The basics of the reconstruction algorithms used for functional cardiac imaging with SPECT do not differ from perfusion imaging (detailed description in [15]). Theoretically, tomographic ERNV allows for better separation of the cavities as compared to planar RNV. This should be especially advantageous for the analysis of RV function and LV volume determination; see below. Geometry based algorithms for the analysis of EF and volumes, as well as

wall motion, are adequate for tomographic ERNV, as the complete ventricular surface is shown, and therefore, no (geometric) assumptions have to be made. Automated software algorithms have been developed for automatic detection of the endocardial contours, allowing for time-efficient analysis [122–124]. Documentation for better determination of EF values compared to conventional methods (RVEF with FP and LVEF with planar ERNV) is, however, not available.

*Cardiac volumes*

LV EDV can be calculated by measuring the counts within the ventricular cavity corrected by attenuation and the distance from ventricle to detector in relation to blood activity from a blood sample [125]. An alternative method is to derive EDV without a blood sample from the ratio of total counts within the cavity (TC) and the maximum pixel count (MPC) together with the area of this pixel ($A_{pix}$) according to Massardo et al. [79]:

$$\mathrm{EDV} = 1.38 \cdot \left( \frac{\mathrm{TC}}{\mathrm{MPC}} \cdot \mathrm{A_{pix}} \right)^{2/3}$$

LV ESV is calculated from EDV and EF.

*Regional wall motion*

The analysis of regional WM is restricted to the areas of the myocardial wall visible in the acquired views. Visual analysis, as well as quantitative analysis of WM from ED to ES, can be performed. For quantitative analysis, the difference in the location of the endocardium in ED and ES along a chosen ray (assumed direction of movement) can be determined where the ray is defined according to a model of myocardial motion. Different models of motion have been created such as

- Motion towards a single point (WM is assumed to be directed towards a single point within the cavity)
- Motion towards the ventricle's long axis (motion within the depicted plane is assumed to be directed towards this long axis)
- Centreline motion (the direction of motion is deduced locally from the ED and ES endocardial contours; the direction of motion is assumed to be perpendicular to a virtual centreline contour lying between the ED and ES endocardial contours so that the distance between the ED contour and centreline contours along this ray is identical to the distance between ES and centreline contours).

*Stress equilibrium radionuclide ventriculography: ejection fraction and wall motion*

Resting and exercise ERNV acquisitions can be analysed for regional left ventricular systolic function. Assessment of regional function is limited during exercise by the presence of only one projection and rather low counts per study. In a healthy individual, LVEF will typically increase during exercise, cf. Section 10 on "Reference values".

## Software features of gated myocardial perfusion SPECT

*General considerations* Functional analysis from perfusion imaging is limited to the LV. Owing to the thin wall, assessment of the RV from perfusion imaging is generally not possible.

The possibility to quantitatively assess LV function at the same time as myocardial perfusion with little additional effort is achieved by sophisticated computer programmes based on automated segmentation of the LV wall. User-interactive segmentation of the myocardium is feasible, but its use in clinical routine is precluded by the high time demand. The exact definitions of the endo- and epicardial contours are not easily deducible from MPS by visual analysis because of the limited resolution of the SPECT methodology, as well as cardiac motion because of respiration and cardiac contractions. Therefore, definition of the endo-/epicardial contours by manual "contour tracing" is unreliable and characterised by poor reproducibility. Automated segmentation algorithms address the problem of limited spatial resolution (partial volume effect) and also have to account for defects in myocardial tracer accumulation (perfusion abnormalities) and possible extracardiac activity (e.g. liver and intestinal hot spots).

Several different algorithms for LV segmentation have been developed and some are commercially available [57–59, 126]. The different algorithms have been shown to yield results that correlate closely with those of RNV, contrast ventriculography, echocardiography and MRI for a large range of ventricular sizes. The reproducibility is generally high. They also correlate well with each other, but limitations have to be accepted:

- The results obtained by different algorithms are not interchangeable.
- LV cavity volumes may be underestimated for small hearts and LVEF overestimated owing to partial volume effect.
- Large perfusion defects may hamper adequate quantification.

*Valve plane* A correct calculation of LV volumes and EF requires the specification of the basal limits of the LV cavity or, in short, the valve plane. Definition of the valve plane is not straightforward, as

- A clear separation of the ventricular cavity from inflow-/outflow tracts is anatomically not feasible.
- Definition of the valve plane from MPS is hampered by the fact that the tracer uptake in the basal part of the septum (membranous portion) does not correspond to the anatomic limit of the ventricle.
- The position of the valve plane is not stable during the cardiac contraction, the motion being closely correlated to the LV EF.

Consequently, definitions of the valve plane from perfusion imaging are approximative, and no consensus has been reached as to the best valve-plane definition. Some software solutions regard the valve plane as perpendicular to the ventricle's long axis; others allow for an oblique valve plane; others, a partly perpendicular partly oblique valve plane. The movement of the valve plane from ED to ES can be restrained to physiologically feasible values in some automated algorithms.

*Endocardial/epicardial contours and regional wall motion* Because of the limited spatial resolution and frequent regional perfusion defects, a simple local edge detection technique is not adequate for the definition of endo-/epicardial contours from gated MPS images. Instead, most methods combine local count information with information about neigbouring tissue and assumptions about shape and properties of the myocardial wall.

General concepts often used

- Radial sampling. Data can be represented in a suitable sampling scheme, where all data are defined on rays that emanate from within the cavity and cross the myocardial wall nearly perpendicularly and nowhere oriented tangentially to the myocardial wall. One sampling scheme models the heart as a hemisphere in the apex and a cylinder in the midventricular and basal portions of the heart; the sampling rays emenate from the centre of the sphere or the long axis of the cylinder, respectively. In another scheme, the rays are oriented perpendicularly to an ellipsoid aligned along the left ventricular long axis.
- Profile fitting. A first local estimate of the wall position can be achieved by fitting a Gaussian curve to the activity profile along a ray across the myocardial wall. Information can be deduced from both the position of the maximum and the width of the curve. However, this curve fitting cannot be expected to be correct in areas with perfusion defects, so that further processing steps are needed.
- Surface interpolation and fitting. A first estimate of local endo- and epicardial positions can be further refined by taking neighbouring areas into account to smooth the estimated heart contour and to bridge local defects. Both interpolation and model-based cost functions are used for this purpose. The different algorithms differ considerably.
- Myocardial volume correction. The fact that the total myocardial volume does not change during contraction can be used to achieve a better estimate of wall thickness in the gated images. Total myocardial volume measured in one frame can be used as a constraint for contour detection in other frames.

There is no general consensus about which approach is the best. All well-validated methods can be used as long as method-specific reference values are used and limitations are recognised.

*Wall thickening*

The low resolution of the SPECT technique compared to the LV wall thickness leads to a partial volume effect that can be utilised to measure regional, systolic WTh non-geometrically using a count-based approach. For a wall thickness less than about twice the spatial resolution of the camera, the regional myocardial activity is not fully recovered in the reconstructed SPECT images. Furthermore, the degree of recovery depends almost linearly on the wall thickness. In the case of gated myocardial SPECT with a typical resolution of 10–20mm (FWHM) and a physiological wall thickness of up to 20mm during systole, this means that systolic WTh translates into an increase of measured activity during systolic movement, which can be easily visualised or quantified from gated SPECT images.

Software features of non-imaging devices

The number of photons emitted from a $^{99m}$Tc-labelled intravascular radiopharmaceutical within the LV is proportional to the LV volume. This effect can be utilised for measurement of LVEF and relative volume changes with non-imaging devices (cf. Section 3 on "Acquisition of radionuclide ventriculography").

*Data analysis*

The nuclear data consist of sequential gamma counts of LV activity sampled approximately 30 times per second. Data

are processed and displayed using software provided by the manufacturer. It is possible to perform averaged summation or single-beat calculations of the gated radionuclide study. Usually, nuclear data obtained in each 10-s to 2-min periods are averaged and gated to reduce the effect of statistical noise and respiratory-induced changes in LV function [48, 73]. A background factor is determined by adjusting the LVEF to that obtained with ERNV. This background value is then applied for the remainder of each individual's data analysis. The use of fixed 70% background subtraction can be applied alternatively [47, 71].

## 10. Reference values

### Introduction

Reference values are indispensable in the evaluation of cardiac function. Few laboratories have developed their own reference values with their own equipment; reference values from the literature are, therefore, used in most centres. However, it must be kept in mind that reference values of cardiac function derived using nuclear methods may vary with the methods used for the acquisition and the software programme used for analysis. Reference values from the literature can, therefore, only be regarded as suggested reference values. The physiological state of the patient at the time of acquisition such as rest or post-stress after different types of stress may also influence the results. Reference values are based on subjects with sinus rhythm. LVEF can be determined, although with less accuracy, in fairly regular arrhythmias, but in more irregular arrhythmias, EF and volume determination become meaningless, as the values vary so markedly from beat to beat. Furthermore, populations from which the reference data are derived may vary: Some include patients with normal outcome of a nuclear cardiology study and otherwise low likelihood of coronary/cardiac disease; some include subjects recruited as healthy volunteers. The sizes of the reference populations are often quite small, accordingly reducing the usefulness of factors like gender and age when defining normal ranges.

Variations in reference values of cardiac volumes will be reduced by normalisation to body surface area (BSA) calculated from the subject's height and weight, the so-called index values (CI, SVI, LVEDVI and LVESVI). Hence, the usefulness of comparison with index values is generally to be preferred to absolute volumes, although index normalisation may be of limited value if the BSA of the patient examined is very low or very high. EF values are independent of BSA.

For evaluation of changes in the same patient (e.g. day-to-day or stress–rest) intra- and inter-day variations should be known. Such variations must be determined locally to be reliable, as they depend both on hardware and software equipment and also include intra- and inter-observer variations.

In these guidelines, some of the most reliable reference values are presented, but other reference values from the literature, not presented here, may be more relevant for some laboratories.

### Right ventricular ejection fraction

As described above, under the specific methods (FP RNV, planar and tomographic ERNV, and gated MPS), RVEF values should be obtained by FP RNV rather than by planar ERNV. Tomographic ERNV is theoretically also a good technique but less validated. MPS cannot be used for RVEF determination.

Pooled data from seven centres using FP technique and seven centres using planar ERNV (Table 5) showed no significant differences in mean reference values assessed by FP technique or ERNV, but no intra-patient comparison was available [127]. No significant differences were observed for RVEF between women and men. According to the authors, however, these groups were too small to draw definite conclusions.

### Left ventricular ejection fraction

*Men vs women, age* Significant differences in mean LVEF values between women and men have been shown in several studies. In the Dallas Heart Study, 1,435 women and 1,183 men were examined with cMRI, and the normal lower limits for women and men were found to be 61 and 55%, respectively [128] (Table 5). The corresponding gated MPS values are lower, but the differences between LVEF values for women and men are the same [129–131]. A small, insignificant difference in LVEF between women and men (65 vs 62%) has been presented for RNV based on pooled data from different centres [127]. LVEF values correlate only weakly with age, and no age-adjustment can be recommended [128, 130].

*Algorithms* Different software has been used for the quantification of gated MPS studies. The QGS method is the method most widely used in studies giving reference values. Several papers in the literature show comparisons between LVEF by QGS based on eight-frame-gated MPS examinations to the corresponding measurements with cMRI, generally considered the gold standard for determining LVEF. These studies generally show an underestimation of LVEF by QGS. One study revealed an underestimation by QGS of 7.4 LVEF% and an underestimation by 4D-MSPECT of 1.6 LVEF%. The corresponding LVEF values calculated with ECT was 2.1 LVEF% higher than that of cMRI [60]. Another comparison between the three software packages showed that 4D-MSPECT and

**Table 5** Right and left ventricular ejection fraction, reference values

| N F/M | Mean F/M | Lower limit F/M | Physiologic state | Population characterised as | Method | Comments | Reference |
|---|---|---|---|---|---|---|---|
| Right ventricular ejection fraction | | | | | | | |
| 365 | 52 | 40 | Rest | Cath normals/volunteers | First pass RNV/ Planar ERNV | Weighted values | [127] |
| Left ventricular ejection fraction | | | | | | | |
| 845/668 | 67/58 | 50/43 | Post-stress (exercise or vasodilator) | Normal stress test and normal perfusion | Gated MPS | 8 frames QGS | [129] |
| 100/78 | 67/59 | 49/41 | Rest or post-stress (exercise or vasodilator) | Low likelihood for CAD | Gated MPS | 8 frames Simpson's rule | [130] |
| 597/824 | 67/59 | 51/43 | Post-stress (exercise or vasodilator) | Low likelihood for CAD and normal perfusion | Gated MPS | 8/16 frames QGS | [131] |
| 1200 | 62 | 50 | Rest | Cath normals/volunteers | FP RNV/ ERNV | Weighted values | [127] |
| 86/214 | 65/62 | 53/46 | Rest | Cath normals/volunteers | FP RNV/ERNV | Weighted values | [127] |

RVEF and LVEF reference values from RNV and Gated MPS studies. For the explanation of other abbreviations, see abbreviation list (before Section 1).
*Cath normals* Patients with a normal coronary angiography, *F/M* females/males, *N* number of subjects, and *QGS* quantitative gated MPS

ECT calculated LVEF values that were 6 and 4 LVEF% higher than those calculated with QGS in patients with normal myocardial perfusion [132].

In gated MPS, the cardiac cycle is usually divided into 8 time frames, sometimes into 16 frames. The lower frame rate resulted in 6.3 lower LVEF% values (95% confidence interval, 5.1–7.5 LVEF%) in a study using the Wakers–Liu circumferential quantification method [133]. Gated MPS is generally done with $^{99m}$Tc-labeled tracers. Some have successfully used $^{201}$Tl and, although the tracer has less than optimum physical properties (low keV), obtained comparable LVEF data [129].

*Rest–stress* LVEF changes from post-stress to rest imaging in a general, outpatient population of patients referred to MPS are modest [134]. A significant decrease in LVEF from rest to (after) stress gives important prognostic information (review by Higgins et al. [135]). During exercise in normal subjects, an increase in LVEF from rest to stress has been found to be 8 LVEF% (range, 3–15%). A slightly higher increase was found for men (10.5%) compared with women (5.3%) [127].

### Left ventricular end-diastolic volume

QGS and 4D-MSPECT have been shown to underestimate LV EDV compared to the corresponding measurements from cMRI with 17 and 10ml, respectively [60]. Another comparison between the three software packages, 4D-MSPECT, ECT and QGS, have shown that 4D-MSPECT and ECT calculate LV EDV values that are 14- and 10-ml higher, respectively, than those calculated with QGS in patients with normal MPS [132] (Table 6).

LV EDV measured by gated MPS with 16 frames was 7ml larger (95% confidence interval, 4.2–9.7ml) than that obtained with 8 frames [133]. In a group of 113 patients, LV EDV was obtained both with $^{201}$Tl at rest and $^{99m}$Tc sestamibi 30–60min after a treadmill test. LV EDV obtained with $^{201}$Tl was slightly but significantly lower than that obtained with $^{99m}$Tc sestamibi (4ml for women and 6ml for men) [129].

### Left ventricular end-systolic volume

LV ESV obtained using QGS and 4D-MSPECT did not differ significantly from the corresponding cMRI measurements [60]. LV ESV measured by gated MPS with 16 frames was 3.6-ml smaller (95% confidence interval, 5.3 to −2.0ml) than that obtained by 8 frames [133]. LV ESV obtained with $^{201}$Tl was slightly but significantly lower than that obtained using $^{99m}$Tc sestamibi (2ml for women and 4ml for men) [129].

### Phase analysis evaluation

According to the reference limit (mean ± 2SD) obtained in control groups, an inter-ventricular asynchrony was considered in the presence of an LV–RV delay >40ms, and an abnormal intra-ventricular synchronism was defined by the presence of SD value >18° (Table 7).

### Summary

Reference values are needed for the interpretation of cardiac, functional data. Although local reference values are preferable because of dependence of equipment, tracers, etc., they are rarely available; hence, the widespread use of reference data from the literature. As several different

**Table 6** Left ventricular end-diastolic and end-systolic volumes, reference values

| N F/M | Mean values F/M | | Upper limits F/M | | Physiologic state | Population characterised as | Comments | Reference |
|---|---|---|---|---|---|---|---|---|
| | **Ml** | **Ml/m$^2$** | **Ml** | **Ml/m$^2$** | | | | |
| Left ventricular end-diastolic volume | | | | | | | | |
| 124/116 | 57/74 | 32/38 | 91/119 | 48/56 | Post-stress(exercise or vasodilator) | Normal stress test and normal MPI | 8 frames; QGS;$^{99m}$TC/$^{201}$Tl | [127] |
| 100/78 | 62/95 | 35/48 | 106/157 | 57/76 | Rest or post-stress (exercise or vasodilator) | Low likelihood for CAD | 8 frames; Simpson's rule; $^{99m}$Tc | [130] |
| 597/824 | 64/95 | 38/49 | 102/149 | 60/75 | Post-stress (exercise or vasodilator) | Low likelihood for CAD and normal MPI | 8/16 frames; QGS; $^{99m}$Tc | [131] |
| Left ventricular end-systolic volume | | | | | | | | |
| 124/116 | 19/29 | 10/15 | 40/55 | 20/27 | Post-stress(exercise or vasodilator) | Normal stress test and normal perfusion | 8 frames; QGS;$^{99m}$TC/$^{201}$Tl | [127] |
| 100/78 | 21/40 | 12/20 | 47/78 | 26/38 | Rest or post-stress (exercise or vasodilator) | Low likelihood for CAD | 8 frames; Simpson's rule; $^{99m}$Tc | [130] |
| 597/824 | 22/41 | 13/21 | 46/75 | 27/39 | Post-stress (exercise or vasodilator) | Low likelihood for CAD and normal perfusion | 8/16 frames; QGS; $^{99m}$Tc | [131] |

LV EDV and LVESV reference values from gated MPS, given in absolute values (ml) and in relation to body surface area (ml/m2). For the explanation of the abbreviations, see abbreviation list (before Section 1).

**Table 7** Phase analysis by ERNV, reference values

| Number of patients | Mean | UL | Physiological state | Population characterised as | Reference |
|---|---|---|---|---|---|
| LV SD (degree) | | | | | |
| 25 | 8 | 15 | Rest | Cardiac patients without structural abnormality or healthy volunteers | [136] |
| 25 | 9 | 18 | Maximum exercise | Cardiac patients without structural abnormality or healthy volunteers | [136] |
| 20 | 22 | 46 | | Healthy volunteers | [137] |
| 56 | 9 | 18 | Rest | Normal ECG and echocardiography | [138] |
| RV SD (degree) | | | | | |
| 20 | 30 | 50 | Rest | Healthy volunteers | [137] |
| 56 | 11 | 19 | Rest | Normal ECG and echocardiography | [138] |
| LV-RV delay (ms) | | | | | |
| 20 | 15 | 41 | Rest | Healthy volunteers | [137] |
| 56 | 14 | 40 | Rest | Normal ECG and echocardiography | [138] |

Mean reference values and standard deviations (SD) of left (LV) and right (RV) ventricular phase analysis from ERNV, given in phase angle degrees and in milliseconds. *UL* Upper limit

reference values have been published for the same variable from different types of reference populations, obtained with different methods and equipment, the local use should adopt as much as possible values retrieved from comparable techniques and sufficiently large reference populations. LVEF and volume reference values in the literature show significant variations with gender; for RVEF, no sex variation is generally reported. Whereas EF data are independent of age and body size, the ranges of reference values for volume data are reduced if expressed in relation to BSA, the index values, which are, therefore, recommended. The intra- and inter-observer variations of the different variables, important for monitoring purposes, can also be found in the literature, but local reproducibility is highly preferred and should be determined.

## 11. Report and image display

### Introduction

*Radionuclide ventriculography* As in all other diagnostic procedures, a written report should be provided at the end of the study, communicating an easily understandable answer to the question asked by the referring physician, including other relevant information and possible clinical implications of the examination and images of the study illustrating the findings described [94, 139–141]. If previous RNV examinations have been performed, it should be described whether any and, in case, which clinically significant changes have occurred compared to previous investigations.

A comment on possible technical problems during acquisition (arrhythmias, poor labelling, insufficient septal separation of the ventricles, etc.) should be added, especially if the technical problem could have an influence on the interpretation of the study.

*Gated MPS* The description is part of the whole MPS description, cf. EANM guidelines [15].

### Description of the study

#### *Ejection fraction*

The most important and most well-documented parameter of an RNV is the LVEF. The EF value may be presented as a fraction value, the more correct way according to its name, or as a percentage value, which is probably used more often. A reference range, cf. the section on reference values, should accompany the presentation of the EF value. If the local reproducibility of the EF value of the laboratory is known, the 95% confidence limits or an SD value should also be included. If the local reproducibility of EF measurements is not available, reference could be given to a value from the literature, cf. the section on reference values. If the EF value is presented as a percentage value (e.g. "LVEF, 56%"), care should be taken to express the confidence limits in a way that cannot be misunderstood, e.g. LVEF = 56% (51–61%), and not in a way like 56 ± 5%. As an alternative, it can be given as a fraction: 0.56 (0.51–0.61) or 0.56 (±0.05).

Other findings that may be included in the report:

- Cardiac morphology, including unusual or abnormal orientation and size of cardiac chambers; extra-cardiac abnormalities (presence of aortic dilatation, extra-cardiac hot spots, etc.).
- Global LV contraction pattern. Visual assessment may suggest asynchronism or global hypokinesia, which may be illustrated by parametric images such as phase and amplitude images.
- Regional LV WM. Segmental contraction, based on visual assessment, can be graded as normal, hypokinetic, akinetic and dyskinetic; the cinematic display of each view (Fig. 4) is required to evaluate all LV segments. Generally, WM abnormalities are reported in decreasing order of severity. Parametric images, such as paradox and phase images, may illustrate in the report dyskinetic vs akinetic regions. It should be noted that, in planar imaging, only a few of the segments are seen without some overlap with the RV.
- Thickness of the pericardial silhouette and LV wall based on visual assessment may suggest pericardial effusion or LV hypertrophy.
- Quantified data, when calculated, may include LV chamber size, stroke volume, cardiac output in milliliters and/or as indices in milliliters per 1.73m$^2$ BSA. Information about reference ranges must be provided together with quantitative data.
- Serial acquisitions. In exercise, pharmacological stress or in pacing RNV studies, any quantitative results should be compared, as well as the regional WM in paired cinematographic displays, and presented together with reference values, preferably obtained by the local department, as significant changes of the parameters are highly dependent on protocol details.
- Right ventricle. In FP RNV, a comment on possible delay in transit of the bolus to or through the right atrium or ventricle and/or lungs is relevant.
- Shunts, regurgitation. In FP studies, scintigraphic signs of right-to-left or left-to-right intra- or extra-cardiac shunts may be noted, as well as tricuspid regurgitation.

### Conclusion(s) of the examination

The conclusion should be brief and addressed to the clinical question, and only include clinically important findings.

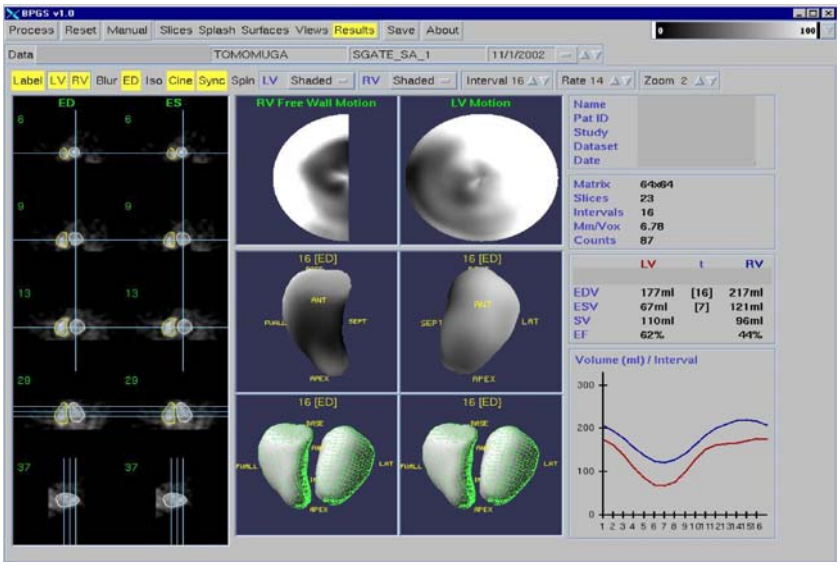


**Fig. 5** Tomographic ERNV: The image of a normal study, obtained with a gamma camera, collimator, energy window, orbit, matrix size and zoom similar to myocardial perfusion SPECT. It displays horizontal slices through the ventricles in end-diastole (outer left column) and end-systole (inner left column). The right image columns show RV in the *right inner column*, LV in the *right outer column*: a polar plot of the free WM (*upper row*) and 3D presentations of the end-diastolic ventricles in the *middle* and *lower rows*. *In the right part of the figure*, values in milliliter are shown for RV and LV volumes, stroke volume, RVEF and LVEF. *In the right lower corner*, TACs for the two ventricles are displayed

## Images accompanying the report

It is generally recommended that an image, either on hard copy or in an electronic version, should accompany the written report. Below are shown two examples (Figs. 5 and 6), one from a tomographic ERNV and the other one from a planar ERNV study. FP studies are usually reframed to an ERNV study for EF calculation, etc.; this may then be presented as an ordinary ERNV. The first-passage of the bolus may also be shown on the image, with TAC from the original bolus passage included in the display accompanying the report.

A typical image report of an RNV study should include (Fig. 6):

– LAO "best septal" end-diastolic and end-systolic images with ROIs superimposed

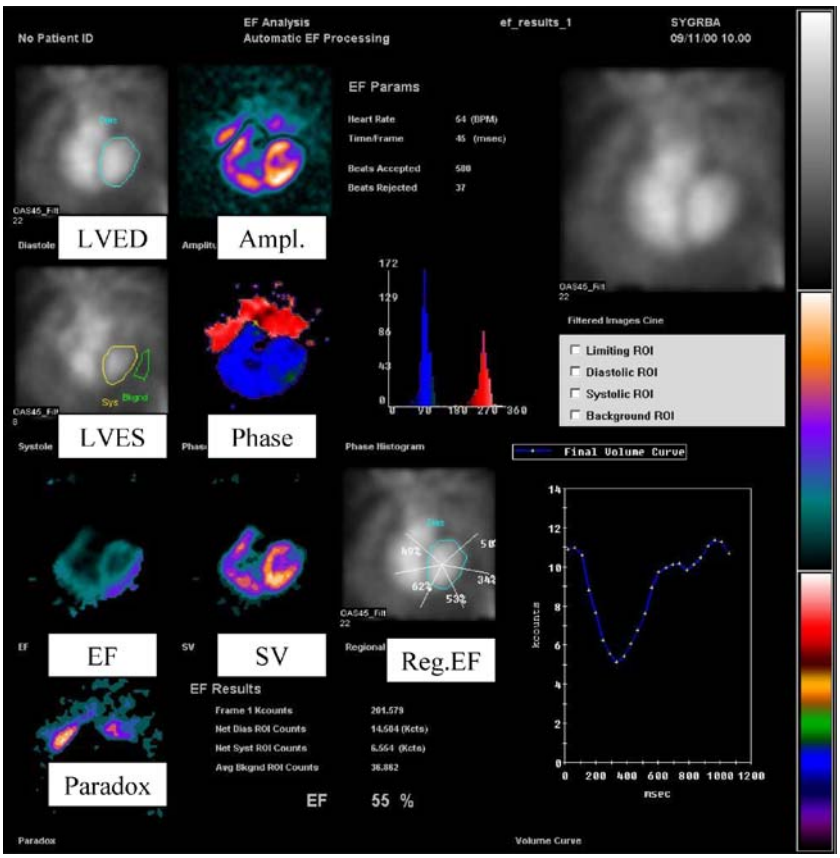


**Fig. 6** The report from an equilibrium radionuclide ventriculography is usually accompanied by an image showing LV end-diastolic (LVED) and end-systolic (LVES) frames, with ROIs superimposed. The LVEF value is seen at the bottom, and the LV TAC is displayed in the lower right corner. Additionally, parametric images are presented from a Fourier analysis: amplitude (*Ampl.*) and phase images, a phase distribution histogram (*in the lower left corner*), stroke volume (*SV*), paradox volume and regional (*Reg.*) EF images

- LV TAC from the "average" cardiac cycle, summed from the accepted cycles of the ERNV
- Global LV EF value
- Average heart rate and number of accepted and rejected beats

It may optionally include (Figs. 1 and 2)

- Parametric images with the phase-distribution histogram, the TAC
- PFR value
- Regional EF values (Fig. 6)
- A histogram of phase against frequency
- Other image projections than the LAO projection (Fig. 6)
- Information from a tomographic or a FP and subsequent equilibrium RNV study including information about both ventricles

LV images are best displayed with a linear black and white scale, which also allows the evaluation of great vessels, whereas parametric images are best displayed in a continuous, colour scale.

*LVEF monitoring* If the indication for the study is monitoring of cardiac function, e.g. during therapy with cardiotoxic drugs, some centres prefer only a minimal report, e.g. showing accumulated LVEF values, limit of a significant LVEF change and the lower reference value of LVEF. The report may then be given without images.

**Acknowledgement** We wish to thank Jenny Sandgren for her devoted efforts with very skillful secretarial assistance.

## References

1. White HD, Norris RM, Brown MA, Takayama M, Maslowski A, Bass NM, et al. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. N Engl J Med 1987;317:850–5.
2. Mahmarian JJ, Shaw LJ, Filipchuk NG, Dakik HA, Iskander SS, Ruddy TD, et al. A multinational study to establish the value of early adenosine technetium-99m sestamibi myocardial perfusion SPECT in identifying a low-risk group for early hospital discharge after acute myocardial infarction. J Am Coll Cardiol 2006;48:2448–57.
3. Schaadt B, Kelbaek H. Age and left ventricular ejection fraction identify patients with advanced breast cancer at high risk for development of epirubicin-induced heart failure. J Nucl Cardiol 1997;4:494–501.
4. Klocke FJ, Baird MG, Bateman TM, Bateman TM, Messer JV, Berman DS, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). J Am Coll Cardiol 2003;42:1318–33.
5. Brown KA, Heller GV, Landin RS, Shaw LJ, Beller GA, Pasquale MJ, et al. Early dipyridamole (99m)Tc-sestamibi single photon emission computed tomographic imaging 2 to 4days after acute myocardial infarction predicts in-hospital and postdischarge cardiac events: comparison with submaximal exercise imaging. Circulation 1999;100:2060–6.
6. Shaw LJ, Hachamovitch R, Berman DS, Marwick TH, Lauer MS, Heller GV, et al. The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients an observational assessment of the value of precatheterization ischemia. J Am Coll Cardiol 1999;33:661–9.
7. Underwood SR, Godman B, Salvani S, Ogle JR, Ell PJ. Economics of myocardial perfusion imaging in Europe—the EMPIRE study. Eur Heart J 1999;20:157–66.
8. Underwood SR, Anagnostopoulos C, Cerqueira M, Ell PJ, Flint EJ, Harbinson M, et al. Myocardial perfusion scintigraphy: the evidence. Eur J Nucl Med Mol Imaging 2004;31:261–91.
9. Sharir T, Germano G, Kavanagh PB, Lai S, Cohen I, Lewin HC, et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. Circulation 1999;100: 1035–42.
10. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.
11. Mitani I, Jain D, Joska TM, Burtness B, Zaret BL. Doxorubicin cardiotoxicity: prevention of congestive heart failure with serial cardiac function monitoring with equilibrium radionuclide angiocardiography in the current era. J Nucl Cardiol 2003;10:132–9.
12. Ewer MS, Vooletich MT, Durand J-B, Woods ML, Davis JR, Valero V, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol 2005;23:7820–6.
13. Kies P, Bootsma M, Bax J, Schalij MJ, van der Wall EE. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: screening, diagnosis, and treatment. Heart Rhythm 2006;3:225–34.
14. Borer JS, Hochreiter C, Herrold EM, Supino P, Aschermann M, Wencker D, et al. Prediction of indications for valve replacement among asymptomatic or minimally symptomatic patients with chronic aortic regurgitation and normal left ventricular performance. Circulation 1998;97:525–34.
15. Hesse B, Tägil K, Cuocolo A, Anagnostopoulos C, Bardiés M, Bax J, et al. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. Eur J Nucl Med Mol Imaging 2005;32:855–97.
16. Amerscan™ Stannous Agent, Technical leaflet. Amersham, 2001.
17. UltraTag RBC, Summary of product characteristics. Mallinckrodt, 2001.
18. Technescan PYP. Summary of product characteristics. Mallinckrodt, 2000.
19. Ellis BL, Sampson CB. Radiolabelling of blood cells—theory and practice. In: Sampson CB, editor. Textbook of radiopharmacy theory and practice. 3rd ed. Amsterdam: Gordon and Breach Science; 1999. p. 83–104.
20. Sampson CB. Complications and difficulties in radiolabelling blood cells: a review. Nucl Med Commun 1996;17:648–58.
21. Zanelli GD. Effect of certain drugs used in the treatment of cardiovascular disease on the in-vitro labelling of red blood cells with $^{99m}$Tc. Nucl Med Commun 1982;3:155–61.
22. International Atomic Energy Agency. Applying radiation safety standards in nuclear medicine no. 40. IAEA safety related publications. Appendix VI: guidance levels for diagnostic procedures. Vienna: IAEA; 2005. p. 101–5.

23. Lassmann M, Biassoni L, Monsieurs M, Franzius C, Jacobs F. The new EANM paediatric dosage card. Eur J Nucl Med Mol Imaging 2007;34:796–8.
24. Millar AM, Wathen CG, Muir AL. Failure in labelling of red blood cells with $^{99m}$Tc: interaction between intravenous cannulae and stannous pyrophosphate. Eur J Nucl Med 1983;8:502–4.
25. Pauwels EKJ, Feitsma RIJ, Blom J. Influence of adriamycin on red blood cell labelling; A pitfall in scintigraphic blood pool imaging. Nucl Med Commun 1983;4:290–5.
26. Sampson CB. Adverse reactions and drug interactions with radiopharmaceuticals. Drug Safety 1993;8:280–94.
27. Lee HB, Wexler JP, Scharf SC, Blaufox MD. Pharmacologic alterations in Tc-99m binding by red blood cells: concise communication. J Nucl Med 1983;24:397–401.
28. International Commission on Radiological Protection. ICRP publication 80: radiation dose to patients from radiopharmaceuticals. Annals of the ICRP, vol. 28. Oxford: Pergamon; 1999. p. 61.
29. Mountford PJ, Lazarus CR, Edwards S. Radiopharmaceuticals. In: Bennet PN, editor. Drugs and human lactation. Amsterdam: Elsevier Science; 1996. p. 609–77.
30. Ahlgren L, Ivarsson S, Johansson L, Mattsson S, Nosslin B. Excretion of radionuclides in human breast milk after the administration of radiopharmaceuticals. J Nucl Med 1985;26:1085–90.
31. Rubow S, Klopper J, Wasserman H, Baard B, van Niekerk M. The excretion of radiopharmaceuticals in human breast milk: additional data and dosimetry. Eur J Nucl Med 1994;21:144–53.
32. International Atomic Energy Agency. Applying radiation safety standards in nuclear medicine No. 40. IAEA safety related publications, Appendix IV: Cessation of breast feeding. Vienna: IAEA; 2005. p. 97–9.
33. Administration of radioactive substances advisory committee. Notes for guidance on the clinical administration of radiopharmaceuticals and use of sealed radioactive sources. National Radiation Protection Board (UK), 2006.
34. Nowotnik DP, Verbruggen AM. Practical and physiochemical aspects of the preparation of $^{99m}$Tc-labelled radiopharmaceuticals. In: Sampson CB, editor. Textbook of radiopharmacy theory and practice. 3rd ed. Amsterdam: Gordon and Breach Science Publishers; 1999. p. 37–56.
35. Vasculocis, Summary of product characteristics. CIS Biointernational; 1996.
36. Technescan HSA, Summary of product characteristics. Mallinckrodt; 2000.
37. Silberstein EB, Ryan J. Prevalence of adverse reactions in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. J Nucl Med 1996;37:185–92, 1064–7.
38. Borer JS. Measurement of ventricular function and volume. In: George A, Beller MD, Zaret BL, editors. Nuclear cardiology: state of the art and future directions. 2nd ed. St. Louis: Mosby; 1999. p. 201–15.
39. Nichols K, DePuey EG, Gooneratne N, Salensky H, Friedman M, Cochoff S. First-pass ventricular ejection fraction using a single-crystal nuclear camera. J Nucl Med 1994;35:1292–300.
40. Williams KA. Measurement of ventricular function with scintigraphic techniques: part I-imaging hardware, radiopharmaceuticals, and first-pass radionuclide angiography. J Nucl Cardiol 2005;12:86–95.
41. Marving J, Høilund-Carlsen PF, Chraemmer-Jørgensen B, Gadsbøll N. Are right and left ventricular ejection fractions equal? Ejection fractions in normal subjects and in patients with first acute myocardial infarction. Circulation 1985;72:502–14.
42. Friedman JD, Berman DS, Borges-Neto S, Hayes SW, Johnson LL, Nichols KJ, et al. Quality Assurance Committee of the American Society of Nuclear Cardiology. First-pass radionuclide angiography. J Nucl Cardiol 2006;13:42–55.
43. Hecht HS, Josephson MA, Hopkins JM, Singh BN. Reproducibility of ERNV in patients with coronary artery disease: response of left ventricular ejection fraction and regional wall motion to supine bicycle exercise. Am Heart J 1982;104:567–74.
44. Iftikhar I, Koutelou M, Mahmarian JJ, Verani MS. Simultaneous perfusion tomography and radionuclide angiography during dobutamine stress. J Nucl Med 1996;37:1306–10.
45. Cates CU, Kronenberg MW, Collins HW, Sandler MP. Dipyridamole radionuclide ventriculography: a test with high specificity for severe coronary artery disease. J Am Coll Cardiol 1989;13:841–51.
46. Dymond DS, Foster C, Grenier RP, Carpenter J, Schmidt DH. Peak exercise and immediate postexercise imaging for the detection of left ventricular functional abnormalities in coronary artery disease. Am J Cardiol 1984;53:1532–7.
47. Tamaki N, Yasuda T, Moore R, Gill JB, Coucher CA, Hutter AM, et al. Continuous monitoring of left ventricular function by an ambulatory radionuclide detector in patients with coronary artery disease. J Am Coll Cardiol 1988;2:669–79.
48. Pace L, Cuocolo A, Stefano ML, Nappi A, Nicolai E, Imbriaco M, et al. Left ventricular systolic and diastolic function measurements using an ambulatory radionuclide monitor: effects of different time averaging on accuracy. J Nucl Med 1993;34:1602–6.
49. Hacker M, Hoyer X, Kupzyk S, Fougere CL, Kois J, Stempfle HU, et al. Clinical validation of the gated blood pool SPECT QBS((R)) processing software in congestive heart failure patients: correlation with MUGA, first-pass RNV and 2D-echocardiography. Int J Cardiovasc Imaging 2006;22:407–16.
50. Daou D, Van Kriekinge SD, Coaguila C, Lebtahi R, Fourme T, Sitbon O, et al. Automatic quantification of right ventricular function with gated blood pool SPECT. J Nucl Cardiol 2004;11:293–304.
51. Kjaer A, Lebech AM, Hesse B, Petersen CL. Right-sided cardiac function in healthy volunteers measured by first-pass radionuclide ventriculography and gated blood-pool SPECT: comparison with cine MRI. Clin Physiol Funct Imaging 2005;25:344–9.
52. Nichols K, Saouaf R, Ababneh AA, Barst RJ, Rosenbaum MS, Groch MW, et al. Validation of SPECT equilibrium radionuclide angiographic right ventricular parameters by cardiac magnetic resonance imaging. J Nucl Cardiol 2002;9:153–60.
53. De BP, Nichols K, Vandenberghe S, Segers P, De WO, Van de WC, et al. Validation of gated blood-pool SPECT cardiac measurements tested using a biventricular dynamic physical phantom. J Nucl Med 2003;44:967–72.
54. De Bondt P, De Winter O, De Sutter J, Dierckx RA. Agreement between four available algorithms to evaluate global systolic left and right ventricular function from tomographic radionuclide ventriculography and comparison with planar imaging. Nucl Med Commun 2005;26:351–9.
55. Akinboboye O, Nichols K, Wang Y, Dim UR, Reichek N. Accuracy of radionuclide ventriculography assessed by magnetic resonance imaging in patients with abnormal left ventricles. J Nucl Cardiol 2005;12:418–27.
56. Chin BB, Bloomgarden DC, Xia W, Kim HJ, Fayad ZA, Ferrari VA, et al. Right and left ventricular volume and ejection fraction by tomographic gated blood-pool scintigraphy. J Nucl Med 1997;38:942–8.
57. Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. J Nucl Med 1995;36:2138–47.
58. Ficaro EP, Quaife RA, Kritzman JN, Corbett JR. Accuracy and reproducibility of 3D-MSPECT for estimating left ventricular ejection fraction in patients with severe perfusion abnormalities (abstract). Circulation 1999;100(Suppl. 1):I26.

59. Faber TL, Cooke CD, Folks RD, Vansant JP, Nichols KJ, DePuey EG, et al. Left ventricular function and perfusion from gated SPECT perfusion images: an integrated method. J Nucl Med 1999;40:650–9.
60. Schaefer WM, Lipke C, Standke D, Kuehl HP, Nowak B, Kaiser HJ, et al. Quantification of left ventricular volumes and ejection fraction from gated $^{99m}$Tc-MIBI SPECT: MRI validation and comparison of the Emory Cardiac Tool Box with QGS and 4D-MSPECT. J Nucl Med 2005;46:1256–63.
61. Kubo N, Mabuchi M, Katoh C, Morita K, Tsukamoto E, Morita Y, et al. Accuracy and reproducibility of left ventricular function from quantitative, gated, single photon emission computed tomography using dynamic myocardial phantoms: effect of pre-reconstruction filters. Nucl Med Commun 2002;23:529–36.
62. Wheat JM, Currie GM. QGS ejection fraction reproducibility in gated SPECT comparing pre-filtered and post-filtered reconstruction. Nucl Med Commun 2006;27:57–9.
63. Hashimoto J, Kubo A, Iwasaki R, Iwanaga S, Mitamura H, Ogawa S, et al. Gated single-photon emission tomography imaging protocol to evaluate myocardial stunning after exercise. Eur J Nucl Med 1999;26:1541–6.
64. Schaefer WM, Lipke CS, Nowak B, Kaiser HJ, Reinartz P, Buecker A, et al. Validation of QGS and 4D-MSPECT for quantification of left ventricular volumes and ejection fraction from gated $^{18}$F-FDG PET: comparison with cardiac MRI. J Nucl Med 2004;45:74–9.
65. Slart RH, Bax JJ, de Jong RM, de Boer J, Lamb HJ, Mook PH, et al. Comparison of gated PET with MRI for evaluation of left ventricular function in patients with coronary artery disease. J Nucl Med 2004;45:176–82.
66. Flotats A, Serra-Grima R, Camacho V, Mena E, Borras X, Estorch M, et al. Left ventricular end-diastolic volume is decreased at maximal exercise in athletes with marked repolarisation abnormalities: a continuous radionuclide monitoring study. Eur J Nucl Med Mol Imaging 2005;32:203–10.
67. Pfisterer N, Regenass S, Müller-Brand J, Burkart F. Ambulatory scintigraphic assessment of transient changes in left ventricular function: a new method for detection of silent myocardial ischaemia. Eur Heart J 1988;9(Suppl N):98–103.
68. Yang LD, Bairey MN, Berman DS, Nichols KJ, Odom-Maryon T, Rozansky A. Accuracy and reproducibility of left ventricular ejection fraction measurements using an ambulatory radionuclide left ventricular function monitor. J Nucl Med 1991;32:796–802.
69. Pace L, Cuocolo A, Nappi A, Nicolai E, Trimarco B, Salvatore M. Accuracy and repeatability of left ventricular systolic and diastolic function measurements using an ambulatory radionuclide monitor. Eur J Nucl Med 1992;19:800–6.
70. Jain D, Joska T, Lee FA, Burg M, Lampert R, Zaret BL. Day-to-day reproducibility of mental stress-induced abnormal left ventricular function response in patients with coronary artery disease and its relationship to autonomic activation. J Nucl Cardiol 2001;8:347–55.
71. Tamaki N, Gill JB, Moore RH, Yasuda T, Boucher CA, Strauss HW. Cardiac response to daily activities and exercise in normal subjects assessed by an ambulatory ventricular function monitor. Am J Cardiol 1987;59:1164–9.
72. Kayden DS, Remetz MS, Cabin HS, Deckelbaum LI, Cleman MW, Wackers FJ, et al. Validation of continuous radionuclide left ventricular function monitoring in detecting silent myocardial ischemia during balloon angioplasty of the left anterior descending artery. Am J Cardiol 1991;67:1339–43.
73. Bairey CN, de Yang L, Berman DS, Rozanski A. Comparison of physiologic ejection fraction responses to activities of daily living: implications for clinical testing. J Am Coll Cardiol 1990;16:847–54.
74. Wolz DE, Flores AR, Grandis DJ, Orie JE, Schulman DS. Abnormal left ventricular ejection fraction response to mental stress and exercise in cardiomyopathy. J Nucl Cardiol 1995;2:144–50.
75. Fearnow EC 3rd, Stanfield JA, Jaszczak RJ, Harris CC, Coleman RE. Factors affecting ventricular volumes determined by a count-based equilibrium method. J Nucl Med 1985;26:1042–7.
76. Wieshammer S, Hetzel M, Hetzel J, Henze E, Clausen M, Hombach V. Reproducibility of left ventricular volume measurements at rest and during bicycle exercise in patients with congestive heart failure: A combined radionuclide and haemodynamic study. Nucl Med Commun 1996;17:591–5.
77. Seldin DW, Esser PD, Nichols AB, Ratner SJ, Alderson PO. Left ventricular volume determination from scintigraphy and digital angiography by a semi-automatic geometric method. Radiology 1983;149:809–13.
78. Gal JA, Grenier RP, Port SC, Dymond DS, Schmidt DH. Left ventricular volume calculation using a count-based ratio method applied to first-passradionucide angiography. J Nucl Med 1992;33:2124–32.
79. Massardo T, Gal RA, Grenier RP, Schmidt DH, Port SC. Left ventricular volume calculation using a count based ratio method applied to multigated radionuclide angiography. J Nucl Med 1990;31:450–6.
80. Thorley PJ, Sheard KL, Rees MR. A comparison of methods for estimating left ventricular from radionuclide ventriculography. Physiol Meas 1993;14:23–32.
81. Nichols K, Humayun N, De Bondt P, Vandenberghe S, Akinboboye OO, Bergmann SR. Model dependence of gated blood pool SPECT ventricular function measurements. J Nucl Cardiol 2004;11:282–92.
82. De Bondt P, Nichols K, Vandenberghe S, Segers P, De Winter O, Van de Wiele C, et al. Validation of gated blood-pool SPECT cardiac measurements tested using a biventricular dynamic physical phantom. J Nucl Med 2003;44:967–72.
83. Sharir T, Germano G, Kang X, Lewin HC, Miranda R, Cohen I, et al. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: Risk stratification by the amount of stress-induced ischemia and the poststress ejection fraction. J Nucl Med 2001;42:831–7.
84. Goris ML, Thompson C, Malone LJ, Franken PR. Modelling the integration of myocardial regional perfusion and function. Nucl Med Commun 1994;15:9–20.
85. Everaert H, Franken PR, Flamen P, Goris M, Momen A, Bossuyt A. Left ventricular ejection fraction from gated SPET myocardial perfusion studies: a method based on the radial distribution of count rate density across the myocardial wall. Eur J Nucl Med 1996;23:1628–33.
86. Faber TL, Stokely EM, Peshock RM, Corbett JR. A model-based four-dimensional left-ventricular surface detector. IEEE Trans Med Imag 1991;10:321–9.
87. Iskandrian AE, Germano G, VanDecker W, Ogilby JD, Wolf N, Mintz R, et al. Validation of left ventricular volume measurements by gated SPECT Tc-99m-labeled sestamibi imaging. J Nucl Cardiol 1998;5:574–8.
88. Achtert AD, King MA, Dahlberg ST, Pretorius PH, LaCroix KJ, Tsui BM. An investigation of the estimation of ejection fractions and cardiac volumes by a quantitative gated SPECT software package in simulated gated SPECT images. J Nucl Cardiol 1998;5:144–52.
89. Lipke CS, Kuhl HP, Nowak B, Kaiser HJ, Reinartz P, Koch KC, et al. Validation of 4D-MSPECT and QGS for quantification of left ventricular volumes and ejection fraction from gated Tc-99m-MIBI SPET: comparison with cardiac magnetic resonance imaging. Eur J Nucl Med Mol Imaging 2004;31:482–90.
90. Thorley PJ, Smith JM. Repeatability of left ventricular ejection fraction and volume measurement for (99)mTc-tetrofosmin gated single photon emission computed tomography (SPECT). Nucl Med Commun 2005;26:345–9.
91. Mazzanti M, Germano G, Kiat H, Kavanagh PB, Alexanderson E, Friedman JD, et al. Identification of severe and extensive

coronary artery disease by automatic measurement of transient ischemic dilation of the left ventricle in dual-isotope myocardial perfusion SPECT. J Am Coll Cardiol 1996;27:1612–20.
92. Bestetti A, Di Leo C, Alessi A, Triulzi A, Tagliabue L, Tarolo GL. Post-stress end-systolic left ventricular dilation: a marker of endocardial post-ischemic stunning. Nucl Med Commun 2001; 22:685–93.
93. Anagnostopoulos C, Harbinson M, Kelion A, Kundley K, Loong CY, Notghi A, et al. Procedure guidelines for radionuclide myocardial perfusion imaging. Heart 2004;90(Suppl 1):i1–10.
94. Scheiner J, Sinusas A, Wittry MD, Royal HD, Machac J, Balon HR, et al. Society of Nuclear Medicine procedure guideline for gated equilibrium radionuclide ventriculography 2002. Society of Nuclear Medicine procedure guidelines, cardiac: gated equilibrium radionuclide ventriculography 3.0. http://www.snm.org.
95. Corbett JR, Akinboboye OO, Bacharach SL, Borer JS, Botvinick EH, DePuey EG, et al. Equilibrium radionuclide angiocardiography. J Nucl Cardiol 2006;13:e56–79.
96. Brateman L, Buckley K, Keim SG, Wargovich TJ, Williams CM. Left ventricular regional wall motion assessment by radionuclide ventriculography: a comparison of cine display with Fourier imaging. J Nucl Med 1991;32:777–82.
97. Walton S, Yiannikas J, Jarritt PH, Brown NJ, Swanton RH, Ell PJ. Phasic abnormalities of left ventricular emptying in coronary artery disease. Br Heart J 1981;46:245–53.
98. Underwood SR, Walton S, Laming PJ, Ell PJ, Emanuel RW, Swanton RH. Patterns of ventricular contraction in patients with conduction abnormality studied by radionuclide angiocardiography. Br Heart J 1984;51:568–74.
99. Muramatsu T, Matsumoto K, Nishimura S. Efficacy of the phase images in Fourier analysis using gated cardiac POOL–SPECT for determining the indication for cardiac resynchronization therapy. Circ J 2005;69:1521–6.
100. Metcalfe MJ, Norton MY, Jennings K, Walton S. Improved detection of abnormal left ventricular wall motion using tomographic radionuclide ventriculography compared with planar radionuclide and single plane contrast ventriculography. Brit J Radiol 1993;66:986–93.
101. Abidov A, Germano G, Hachamovitch R, Berman DS. Gated SPECT in assessment of regional ad global left ventricular function: major tool of modern nuclear imaging. J Nucl Cardiol 2006;13:261–79.
102. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539–50.
103. Wackers FJTh. Equilibrium radionuclide angiograhy. In: Gerson MC, editor. Cardiac nuclear medicine. 3rd ed. New York: McGraw Hill; 1997. p. 315–45.
104. Arrighi JA, Soufer R. Left ventricular diastolic function: physiology. Methods of assessment, and clinical significance. J Nucl Cardiol 1995;2:525–43.
105. Clements IP, Sinak LJ, Gibbons RJ, Brown ML, O'Connor MKl. Determination of diastolic function by radionuclide ventriculography. Mayo Clin Proc 1990;65:1007–19.
106. Bonow RO, Vitale DF, Bacharach SL, Maron BJ, Green MV. Effects of aging on asynchronus left ventricular regional function and global ventricular filling in normal human subjects. J Am Coll Cardiol 1988;11:50–8.
107. Bonow RO, Bacharach SL, Green MV, Kent KM, Rosing DR, Lipson LC, et al. Impaired left ventricular diastolic filling in patients with coronary artery disease: assessment with radionuclide angiography. Circulation 1981;64:315–23.
108. Parker JA, Uren RF, Jones AG, Maddox DE, Zimmerman RE, Neill JM, et al. Radionuclide left ventriculography with the slant hole collimator. J Nucl Med 1977;18:848–51.
109. Gunter DL. Collimator Design for Nuclear Medicine. In: Wernick M, Aarsvold J, editors. Emission tomography: the fundamentals of PET and SPECT. San Diego, London: Elsevier Academic; 2004. p. 153–68.
110. Liu YH, Lam PT, Sinusas AJ, Wackers FJ. Differential effect of 180 degrees and 360 degrees acquisition orbits on the accuracy of SPECT imaging: quantitative evaluation in phantoms. J Nucl Med 2002;43:1115–24.
111. Friedman JD, Berman DS, Kiat H, Bietendorf J, Hyun M, Van Train KF, et al. Rest and treadmill exercise first-pass radionuclide ventriculography: validation of left ventricular ejection fraction measurements. J Nucl Cardiol 1994;1:382–8.
112. Bailey DL, Hutton BF, Walker PJ. Improved SPECT using simultaneous emission and transmission tomography. J Nucl Med 1987;28:844–51.
113. Tan P, Bailey DL, Meikle SR, Eberl S, Fulton RR, Hutton BF. A scanning line source for sumultaneous emission and transmission measurements in SPECT. J Nucl Med 1993;34:1752–60.
114. Celler A, Sitek A, Stoub E, Hawman P, Harrop R, Lyster D. Multiple line source array for SPECT transmission scans: simulation, phantom and patient studies. J Nucl Med 1998; 39:2183–9.
115. Hasegawa BH, Lang TF, Brown JK, Gingold EL, Reilly SM, Blankespoor SC, et al. Object-specific attenuation correction for SPECT with correlated dual-energy X-ray CT. IEEE Trans Nucl Sci 1993;40:1242–52.
116. Blankespoor SC, Xu X, Kaiki K, Brown JK, Tang HR, Cann CE. Attenuation correction of SPECT using X-ray CT on an emission-transmission CT system: myocardial perfusion assessment. IEEE Trans Nucl Sci 1996;43:2263–74.
117. Schelbert HR, Verba JW, Johnson AD, Brock GW, Alazraki NP, Rose FJ, et al. Nontraumatic determination of left ventricular ejection fraction by radionuclide angiocardiography. Circulation 1975;51:902–9.
118. Germano G, Kavanagh PB, Su HT, Mazzanti M, Kiat H, Hachamovitch R, et al. Automatic reorientation of 3-dimensional transaxial myocardial perfusion SPECT images. J Nucl Med 1995;36:1107–14.
119. Mullick R, Ezquierra NF. Automatic determination of left ventricular orientation from SPECT data. IEEE Trans Med Imag 1995;14:88–99.
120. Ratib O, Henze E, Schon H, Schelbert HR. Phase analysis of radionuclide ventriculograms for the detection of coronary artery disease. Am Heart J 1982;104:1–12.
121. Wu J, Takeda T, Toyama H, Ajisaka R, Masuoka T, Watanabe S, et al. Phase changes caused by hyperventilation stress in spastic angina pectoris analyzed by first-pass radionuclide ventriculography. Ann Nucl Med 1999;13:13–8.
122. Faber TL, Stokely EM, Templeton GH, Akers MS, Parkey RW, Corbett JR. Quantification of three-dimensional left ventricular segmental wall motion and volumes from gated tomographic radionuclide ventriculograms. J Nucl Med 1989;30:638–49.
123. Bartlett ML, Srinivasan G, Barker WC, Kitsiou AN, Dilsizian V, Bacharach SL. Left ventricular ejection fraction: comparison of results from planar and SPECT gated blood-pool studies. J Nucl Med 1996;37:1795–9.
124. van Kriekinge SD, Berman DS, Germano G. Automatic quantification of left ventricular ejection fraction from gated blood pool SPECT. J Nucl Cardiol 1999;6:498–506.
125. Links JM, Becker LC, Shindledecker JG, Guzman P, Burow RD, Nickoloff EL, et al. Measurement of absolute left ventricular volume from gated blood-pool studies. Circulation 1982;65:82–91.

126. Stegger L, Biedenstein S, Schäfers KP, Schober O, Schäfers MA. Elastic surface contour detection for the measurement of ejection fraction in myocardial perfusion SPET. Eur J Nucl Med 2001; 28:48–55.
127. Pfisterer ME, Battler A, Zaret BL. Range of normal values for left and right ventricular ejection fraction at rest and during exercise assessed by radionuclide angiocardiography. Eur Heart J 1985;6:647–55.
128. Chung AK, Das SR, Leonard D, Peshock RM, Kazi F, Abdullah SM, et al. Women have higher left ventricular ejection fractions than men independent of differences in left ventricular volume. The Dallas Heart Study. Circulation 2006;113:1597–604.
129. Ababneh AA, Sciacca RR, Kim B, Bergmann SR. Normal limits for left ventricular ejection fraction and volumes estimated with gated myocardial perfusion imaging in patients with normal exercise test results: influence of tracer, gender, and acquisition camera. J Nucl Cardiol 2000;7:661–8.
130. Rozanski A, Nichols K, Yao SS, Malholtra S, Cohen R, DePuey EG. Development and application of normal limits for left ventricular ejection fraction and volume measurements from $^{99m}$Tc-sestamibi myocardial perfusion gates SPECT. J Nucl Med 2000;41:1445–50.
131. Sharir T, Kang X, Germano G, Bax JJ, Shaw LJ, Gransar H, et al. Prognostic value of poststress left ventricular volume and ejection fraction by gated myocardial perfusion SPECT in women and men: gender-related differences in normal limits and outcomes. J Nucl Cardiol 2006;13:495–506.
132. Lum DP, Coel MN. Comparison of automatic quantification software for the measurement of ventricular volume and ejection fraction in gated myocardial perfusion SPECT. Nucl Med Commun 2003;24:259–66.
133. Navare SM, Wackers FJ, Liu YH. Comparison of 16-frame and 8-frame gated SPET imaging for determination of left ventricular volumes and ejection fraction. Eur J Nucl Med Mol Imaging 2003;30:1330–7.
134. Ramakrishna G, Miller TD, Hodge DO, O'Connor MK, Gibbons RJ. Differences in left ventricular ejection fraction and volumes measured at rest and poststress by gated sestamibi SPECT. J Nucl Cardiol 2006;13:668–74.
135. Higgins JP, Higgins JA, Williams G. Stress-induced abnormalities in myocardial perfusion imaging that are not related to perfusion but are of diagnostic and prognostic importance. Eur J Nucl Med Mol Imaging 2007;34:584–95.
136. Underwood SR, Walton S, Laming PJ, Ell PJ, Emanuel RW, Swanton RH. Quantitative phase analysis in the assessment of coronary artery disease. Br Heart J 1989;61:14–22.
137. Fauchier L, Marie O, Casset-Senon D, Babuty D, Cosnay P, Fauchier JP. Interventricular and intraventricular dyssynchrony in idiopathic dilated cardiomyopathy: a prognostic study with fourier phase analysis of radionuclide angioscintigraphy. J Am Coll Cardiol 2002;40:2022–30.
138. Marcassa C, Campini R, Verna E, Ceriani L, Giannuzzi P. Assessment of cardiac asynchrony by radionuclide phase analysis. Correlation with ventricular function in patients with narrow or prolonged QRS Interval. Eur J Heart Failure 2007;9:484–90.
139. Wackers F. Intersocietal Commission for the Accreditation of Nuclear Medicine Laboratories (ICANL) position statement on standardization and optimization of nuclear cardiology reports. J Nucl Cardiol 2000;7:397–400.
140. Cerqueira MD. The user-friendly nuclear cardiology reports: what needs to be considered and what is included. J Nucl Cardiol 1996;3:350–5.
141. Hendel RC, Wackers FJ, Berman DS, Ficaro E, DePuey EG, Klein L, et al. American Society of Nuclear Cardiology consensus statement: reporting of radionuclide myocardial perfusion imaging studies. J Nucl Cardiol 2006;13:e152–6.