University of Twente, Robotics and Mechatronics

Development of a myocardial perfusion phantom

Gijs de Vries, s1854526

Revision 0.210

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Preface

The system requirements specify all the requirements for the myocardial perfusion phantom. These requirements are based on research and interviews with stakeholders.

G.J. (Gijs) de Vries
Enschede, 7th of January 2019

Version

Requirement	Old description	Date
R0.1	Initial version. Discussed in progress meeting of 2019/01/15.	2019/01/15
R0.2	Added following items: •TR-PR02, TR-PR03, TR-PR04, TR-PR05, TR-PR06, TR-PR07, TR-PR08, TR-PR09, TR-PR10 •TR-ER02, TR-ER03 •TR-IC04, and TR-IC05 •Added appendices C & D.	2019/01/16
R0.21		2019/01/18
R0.22	Added following items: •TR-IC03 A) through E). •TFR-SIM04 A) through E) •TR-PR02 A) through E).	2019/01/20
R0.23	Added following items: •TFR-SIM05 A) through C).	2019/01/23
R0.24	Modified: •Section 2.2.1, to correspond to interview at ZGT. Added following items: •Figure 3.3, 3.4, and 3.5 Removed following items: •FR08 (combined with FR07) Inserted following items: •TFR-SIM04 B) & C). Other requirements are shifted down.	2019/01/28
R0.25	Modified: •Section 2.2.2, rephrased. Removed following items: •TFR-SIM04 E), combined with TFR-SIM04 D), AIF initially in left atrium but alternatively in left ventricle. Added following items: •TFR-GF09.	2019/01/29
R0.26	Textual (argumentative) requirements are separated from the quantitative requirements. Modified following items:	2019/01/30

Requirement	Old description	Date
	•Caption of figure 2.2 to make it clear that it is not definitive. •Business model, rephrased and added business cases as discussed in work meeting of January 29, 2019. Added following items: •TFR-GFQ03, TFR-GFQ04, TFR-GFQ09, TFR-GFQ10.	
R0.27	Textual (argumentative) requirements are separated from the quantitative requirements. Removed following items: •TR-PRT03 A) and D), double requirements.	2019/01/31
R0.28	Textual (argumentative) requiremens are separated from the quantitative requirements. Added following items: •TR-SQ03 •TFR-SIMT04 Removed following items: •TR-ERT03, the patient chair is in supine (flat) position and should provide enough space for the set-up.	2019/02/01
R0.29	Renamed environmental requirements to external requirements; the requirements that are specified from the outside of the system. Added following items: •TR-PRQ07	2019/02/04
R0.210	Added technical block diagram. Removed following items: •TFR-ICT05 B), tracer injection parameters are now specified in TFR-ICQ04, TFR-ICQ05, and TFR-ICQ06. Added following items: •TFR-ICQ04, TFR-ICQ05, TFR-ICQ06.	2019/02/05

Changelog

Requirement	Old description	Change reason
TR-IC01	A variable amount of contrast can be injected.	Rephrased.
TFR-SIM01	An Arterial Input Function (AIF) must be extractable from either the aorta or the left ventricle chamber.	The AIF, in the D-SPECT software, is taken from the left ventricle. This requirement is moved to TFR-SIM04.
TFR-SIM04	Multiple chambers, or areas, should be present, such that ischaemic and non-inschaemic tissue can be visualised simultaneously. Typical software divide the heart into 17 chambers.	Rephrased due to misunderstanding of the 17 section model.
TR-PR10	The phantom's chambers must match the dimensions of an average human heart, between 60-90x30-50x60-90mm [LxWxD]	Sizes are specified for the ventricles.
TR-PR02	The phantom must be anatomically correct; four heart chambers, myocardium around the chambers, arrow shaped bottom.	Rephrased after interview at ZGT.
TFR-SIM05	Phantom's compartment model should match the currently practised protocol. Does the tracer diffuse, is it trapped in tissue et cetera.	Rephrased and linked to contrast section.
FR03	The high flow should be suitable for an AIF, either in a ventricle chamber or an aorta depending on the clinical software.	The D-SPECT software extracts the AIF in the left atrium.
FR04	Cardiac defects should be simulated such that the complex relation between stenotic and non-stenotic arteries is modelled.	Rephrased.
FR05	The phantom must be able to visualise both control and stenotic areas, similar to clinical scans.	Rephrased, it should be compatible with the 17 segment model.
FR06	The phantom must initially simulate the compartment model typically used in clinical scans, but be flexible enough such that other compartment models are achievable.	Rephrased to be more specific.
FR07	The contrast agent should be equivalent to that used in clinical scans.	Rephrased and combined with FR08 to be more global.
TFR-SIM04 A)	The three coronary arteries should be present (RCA, LAD, LCx) and connected to a myocardium.	Rephrased to make it more clear.
TFR-SIM04 F)	The myocardium has a longitudinal cross-sectional shape of a horseshoe.	Rephrased to be more specific.
TFR-SIM04 G)	The myocardium has a transverse cross-sectional shape of a circle.	Rephrased to be more specific.

Requirement	Old description	Change reason
TFR-SIM04 D)	An ROI can be taken in the left ventricle.	Combined with TFR-SIM04 E), AIF is taken in left atrium. If it has poor results, the AIF's ROI can be moved to the left ventricle.
TFR-SIM04 E)	An AIF can be taken from the left atrium.	Removed, combined with TFR-SIM04 D).
TR-PR02 A)	In correspondence with requirements TFR-SIM04 D) and E)	TFR-SIM04 requirements were modified, therefore TR-PR02 is modified in accordance.
TFR-GF03	Minimum achievable upper limit of myocardial perfusion is 300 mL/min/100g.	Added more specificity for stress perfusion.
TFR-GF04	Minimum achievable lower limit of myocardial perfusion is 60 mL/min/100g.	Added more specificity for rest perfusion.
FR05	The phantom must be able to visualise (and measure) the 17-segment cardiac model.	17 active segments will be too much for the initial version.
FR03*	The high flow should be suitable for an AIF extracted from the left atrium.	Rephrased to be more specific.
FR07	The contrast protocol must be equivalent to that used in clinical scans with D-SPECT.	For SPECT, the terminology is "tracer" in stead of "contrast".
TR-PR01	The phantom, and its set-up, must fit on the D-SPECT's chair.	The phantom itself must fit on the chair and in the imaging area. However, the set-up surrounding the phantom (flow generators, measurement systems et cetera) do not necessaries
TFR-ICT04	Tracer injection is reproducible.	Tracer injection is reproducible using an infusion pump. Too much variation exists when tracer is injected manually.
TR-PRT01	The phantom is to be placed inside the QRM TRX-116, see TR-PRQ01.	The phantom's left ventricle is to be placed inside the thorax phantom as opposed to the entire phantom.

Requirement	Old description	Change reason
TR-PRT02	The phantom must fit on the D-SPECT seating in the imaging area.	The left ventricle must be in the imaging area as opposed to the entire phantom.
TFR-GFT01	A constant flow is to be generated, i.e. non-pulsatile.	Flow must be constant and variable.

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1 Introduction

Myocardial Perfusion Imaging (MPI), or, simply put, the imaging of the blood flow in the heart muscle, plays an important role in diagnosing heart failure or detecting Coronary Artery Disease (CAD). Imaging systems like Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Single-Photon Emission Computed Tomography (SPECT), or Positron Emission Tomography (PET) can visualise a (radioactive) contrast bolus in the supplying arteries and in underlying myocardial tissue, whose flow can give an indication of narrowed or blocked blood vessels.

Many variations in the visualisation process of myocardial perfusion, including variations in hard- and software, can (significantly) influence the outcome and in turn have consequences for patient treatment. These variations need to be validated against a well-known baseline.

A myocardial perfusion phantom will be developed that is able to simulate the blood flow in the heart muscle, i.e. the myocardium, and is able to mimic cardiac defects like (significant) stenosis.

Document overview

[todo] This section

Abbreviations

AIF Arterial Input Function

CAD Coronary Artery Disease

CT Computed Tomography

HLA Horizontal Longitudinal Axis

LA Left Atrium

LV Left Ventricle

MPI Myocardial Perfusion Imaging

MRI Magnetic Resonance Imaging

MV Maximal Vasodilation

PET Positron Emission Tomography

RA Right Atrium

ROI Region of Interest

RV Right Ventricle

SA Short Axis

SPECT Single-Photon Emission Computed Tomography

VLA Vertical Longitudinal Axis

2 Functional system overview

This chapter goes into detail on the functional aspects of the myocardial perfusion phantom.

2.1 Drivers

Many factors influence the outcome of MPI. Some of these factors are:

Tracer	**Patient**	**Technology**	**Software**
- Concentration,	- Breathing artefacts,	- Modality,	- Package,
- Volume,	- Cardiac motion,	- Spatial resolution,	- Mathematical model,
- Molecule size,	- BMI.	- Temporal resolution.	- Filters,
- Injection speed.			- ROI.

The strength of a phantom is that small modifications, for example, in contrast concentration or volume, or the mathematical model, can be directly mapped to the outcome. It provides insight into dependent and independent factors in perfusion imaging.

Current phantoms either require modifications to software packages or do not model defects in a physiological way. Defects are typically modelled by reducing the flow through the myocardium by reducing the pump rate, effectively ignoring the complex relation between stenotic and non-stenotic arteries. Therefore, a myocardial perfusion phantom is needed that is compatible with clinical software and is able to mimic cardiac defects in a physiological way. This will increase the similarity with patient studies resulting in more reliable validation.

In addition to being a tool for validation of scanners and/or software packages, the phantom can be used for educational and training purposes to demonstrate the impact of hard- and software variables (sampling rate, Region of Interest (ROI), mathematical model), patient variables (BMI, blood flow and -pressure), tracer variables (concentration, type, injection speed), and many more.

2.2 Approach

The V-Model defines the project's development cycle.

2.2.1 Concept of operations

Is the D-SPECT's dynamic scanning, in comparison with other modalities (CT, MRI, PET, or SPECT), suitable for quantitative myocardial perfusion imaging?

Quantitative flow measurements is made possible due to dynamic scanning. Dynamic scanning is not a newly emerged technique, it has been used with CT in past research. Due to the solid-state detectors (Cadmium-Zinc Telluride), dynamic scanning is made possible for SPECT. The D-SPECT is relatively new in the Netherlands. However, it has been employed in Japan, Canada, France, and Great-Britain. The D-SPECT is a highly specialised cardiac system. Due to the relatively small patient population, clinics often choose more all-purpose systems. The D-SPECT is very patient friendly due to its design in contrast to alternatives, e.g. GE uses a gantry design.

CT is a well established modality with the highest spatial resolution. However, its largest drawback is that the radiation dose is directly proportional to the number of images, therefore increasing the likelihood of complication due to radiation exposure. MRI does not rely an ionising radiation, but its lower temporal resolution makes it less suitable for dynamic imaging. SPECT and PET use radioactive tracers to image blood flow, thus exposing the patient to some degree of radiation. However, it is not directly proportional to the amount of images taken and is therefore less dangerous than CT.

In addition, traditional SPECT is, on average, 22% less expensive than the current gold standard, PET. D-SPECT is supposed to be even less expensive and faster. Furthermore, significant dose reduction, due to more sensitive solid-state detectors, reduces the strain and risk for patients. In addition, these solid-state detectors improve the image resolution.

In summary, although the D-SPECT is relatively new in the Netherlands, it is more widely employed in Japan, Canada, France, and Great-Britain. The highly cardiac specialised system, its patient friendly design, the ability to scan faster and more accurate at significant dose reductions, make the D-SPECT suitable for quantitative myocardial perfusion imaging.

2.2.2 What must the myocardial perfusion phantom be able to simulate to validate quantitative MPI?

The phantom must be compatible with clinical practice, i.e. use clinical protocols and hard-/software. Patients are scanned in a D-SPECT scanner while lying down. The scans are evaluated using 4DM software.

The phantom must be suitable for an ROI in the left atrium for AIF extraction. However, in case of poor results, the ROI can be reshaped and moved to the left ventricle. The software determines the perfusion in 17 areas, i.e. the 17-segment heart model, of the myocardium, at a basal, mid and apical level, and at the apex. These segments are supplied via branches of the three coronary arteries, i.e. the RCA, LAD, and LCx. 4DM calculates individual flow rates for each segment. Therefore, the phantom should contain 17 segments where each segment's flow can be measured.

A single flow source is to be used that supplies the RCA, LAD, and LCx. From an anatomical viewpoint, the coronary arteries are supplied from the aorta. The phantom could mimic this anatomical structure, which, from a practical viewpoint, is impractical. Instead, it is possible to supply the coronary arteries from a dedicated flow source significantly decreasing the total volume of liquid being displaced. Care must be taken such that the ratio of contrast remains equivalent. Since the entire myocardium is supplied by three coronary arteries, stenosis in one of the arteries, or its branches, results in different flow behaviour which cannot be mimicked by reducing the overall flow to the myocardium alone.

Every tracer behaves differently. For D-SPECT, Technetium (^{99m}Tc) Tetrofosmin is used. This tracer is absorbed by the myocardium. The phantom will thus have to mimic this behaviour in the myocardium.

2.3 Business model

Dynamic scanning yield quantitative results, i.e. absolute perfusion rates, which require proper validation. Phantom studies are, to a high degree, suitable for such purpose. An added benefit of these studies, is that it provides insight into the effect of different parameters on the outcome, which in turn influences patient treatment. These insights can be used for calibration or protocol optimisation, e.g. tracer protocol. Examples would be determining optimal (patient dependable) activity or injection speed.

In short, the phantom can be used for educational and training purposes, as well as for calibration or optimisation.

The phantom will distinguish itself from other phantoms due to its more true-to-nature design, ability to physiologically mimic cardiac defects, and the possibility of modelling different compartment models.

The primary focus remains on the current application of MPI as performed at the ZGT in Hengelo, Overijssel.

2.4 Requirements

[todo] Verify the AIF requirements.

The functional requirements are summarised in table 2.1.

Table 2.1: Functional requirements

This table summarises the functional requirements for the prototype myocardial perfusion phantom.

Requirement number	Description
FR01	The phantom must be able to simulate blood flow, either using water of blood-mimicking fluid, at high flow rates (aortic flow).
FR02	The phantom must be able to simulate blood flow, either using water or blood-mimicking fluid, at low flow rates (myocardial flow).
FR03*	An AIF can be extracted from the left atrium, or alternatively from the left ventricle.
FR04	Cardiac defects must simulate the complex relation between stenotic and non-stenotic arteries.
FR05	The phantom must be able to visualise (and measure) at least two active segments of the 17-segment ventricle model.
FR06	The phantom must use a 2-compartment model (simulating contrast uptake in tissue).
FR07	Tracer protocol must be equivalent to that used in clinical scans with D-SPECT.
~~FR08~~	~~Contrast should be mixed equivalently to contrast mixing in patients.~~

** Depending on the flexibility of the clinical software.*

2.5 Business and system use cases

The myocardial perfusion phantom is used by researchers with varying goals. Primarily, the phantom set-up is a tool to validate perfusion imaging hard- and software and to educate on independent and dependent factors, see section 2.1. The researcher should be able to adjust the blood flow, both in the myocardium and in the aorta, and be able to set a cardiac defect.

Please note, setting the imaging and contrast parameters are not part of the phantom itself.

2.6 Architectural overview

A schematic overview of the flow set-up is shown in figure 2.2. The set-up consists of a flow generating system, e.g. mechanical pumps or pressure based, to generate the required aortic and myocardial flow, measuring systems, e.g. flow and pressure sensors, and the phantom itself, simulating the heart. The flow is controlled by means of a control system, over which the user has control. The flow parameters, i.e. flow and pressure, are measured by sensors which are monitored by a monitoring system. The monitoring system and control system cooperate such that user parameters are maintained. Figure 2.2 shows a distinction between high and low flow, which is not a requirement. Low flow can be created by means of pressure difference in high and low flow circuit; increasing pressure in low flow circuit results in less volume passing through.

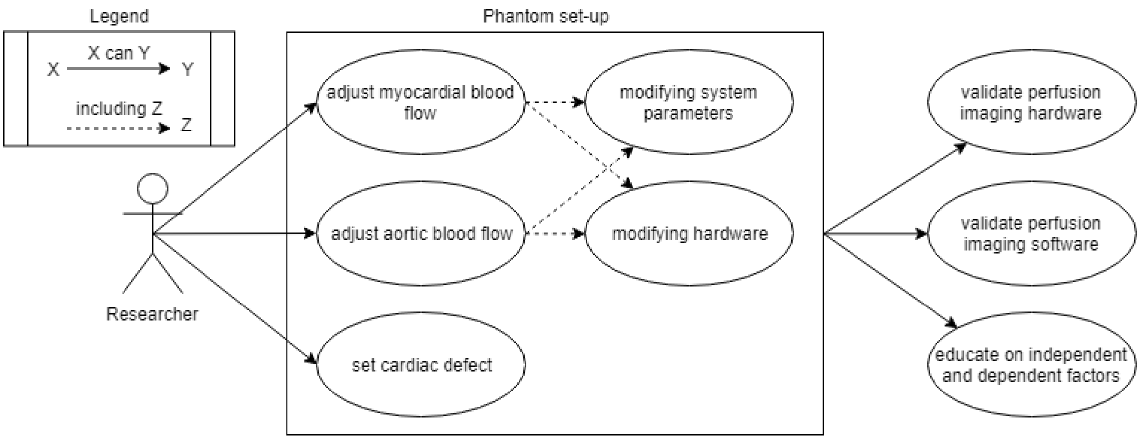

Figure 2.1: Use case diagram for the prototype myocardial perfusion phantom

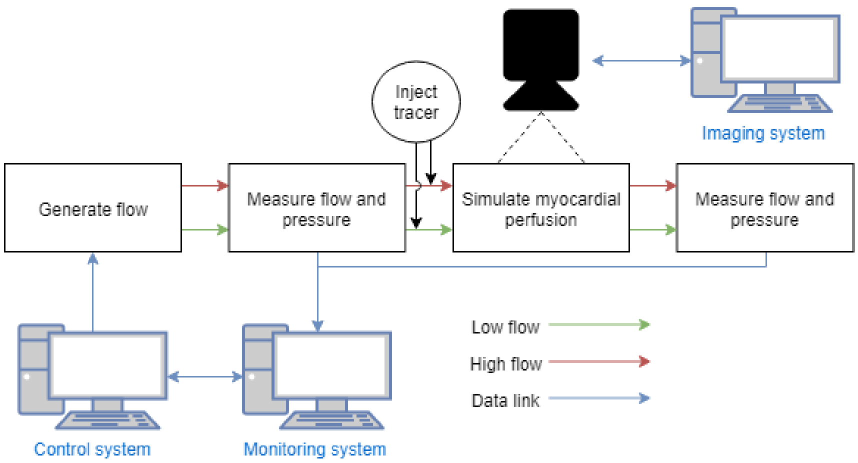

Figure 2.2: Functional architecture for the myocardial perfusion set-up, **not yet definitive.**

3 Technical system overview

3.1 System

The following section defines the phantom as described by Van Meurs (2011).

3.1.1 Organ

The organ to be simulated is the myocardium of the left ventricle, more specifically the blood flow in the myocardium. The left ventricle has a Horizontal Longitudinal Axis (HLA) and Vertical Longitudinal Axis (VLA) cross-sectional shape of a horseshoe and a Short Axis (SA) cross-sectional shape of a circle, see figure 3.1. Quantitative data on blood flow is available in previous research by Uren et al. (1994); Chiribiri et al. (2013); Ho et al. (2014); Slart (2015). Heart size indications are available in previous research by Lin et al. (2008); Maceira et al. (2006a,b).

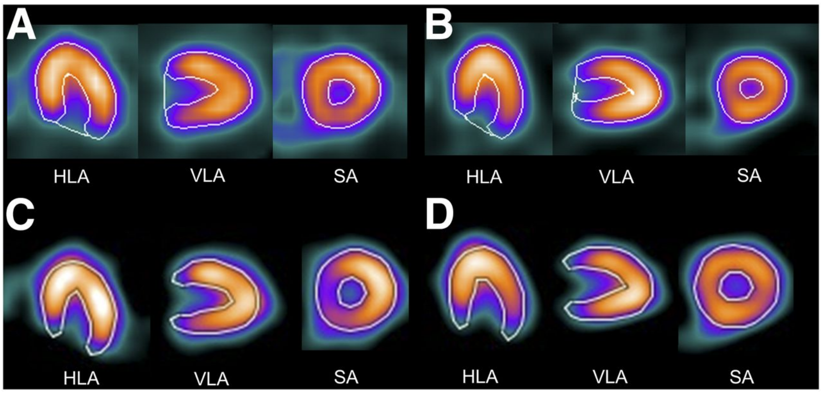

Figure 3.1: Ventricle shapes in different planes(Yoneyama et al., 2017)

3.1.2 Population

The heart phantom will be designed for average adults of both genders with ages between 18 and 79. The population consisted of patients with and without CAD.

3.1.3 Physiological states

The heart will be simulated in both a resting state and in a stress state while the "patient" is in a supine position. The D-SPECT captures intensity images based on gamma rays caused by the radioactive decay of a tracer which is injected intravenously. The D-SPECT does not capture any information other than intensity information from gamma rays. Therefore the composition of the fluid is of less importance; water is most practical.

3.1.4 Pathologies

The phantom aims to simulate the perfusion in the myocardium of healthy patients and of patients with CAD, more specifically stenosis of the coronary arteries or its subsequent branches. Stenosis in one of the arteries will have an impact on the overall flow behaviour (higher pressure, less overall flow, more flow to non-stenotic arteries) and thus requires the phantom to mimic the same behaviour.

3.1.5 Clinical signs and monitored variables

Blood flow is the most important variable to be monitored as these will be compared to the quantitative results produces by the processing software of the D-SPECT's images. Blood pressure must be monitored for indicative purposes. Depending on the phantom's final design, blood pressure can be critical for the simulation of the myocardial perfusion.

3.1.6 Critical incidents

No critical incidents will be simulated.

3.1.7 Interventions

No interventions will be simulated.

3.1.8 Overall block diagram

Figure 3.2 shows an overview of all systems, how they are separated, and their interrelations. A distinction is made between four key elements; the flow set-up, the phantom, the imaging system, and external systems. The generation of an artificial heartbeat and the injection of the tracer are carried out externally and do not require development. Additionally, the imaging system (D-SPECT) with analysis software (4DM) do not require development since it concerns off-the-shelf hard-/software. The flow set-up and the phantom do require development.

The flow is generated for different physiological states for high and low flows, i.e. for stress and rest. A closed-loop circuit monitors and controls the flow for optimal accuracy. The tracer is injected and flows to the phantom where the myocardial perfusion is mimicked. The contaminated water flows out of the phantom such that it can de disposed. Optionally, if the tracer can be filtered from the contaminated water, a closed, recirculating system can be fabricated; greatly reducing water waste. The tracer undergoes radioactive decay that results in the emission of gamma rays, which are picked up by the D-SPECT's detectors. The resulting intensity images can be reconstructed to form cross-sectional images which in turn are used to quantify the blood flow.

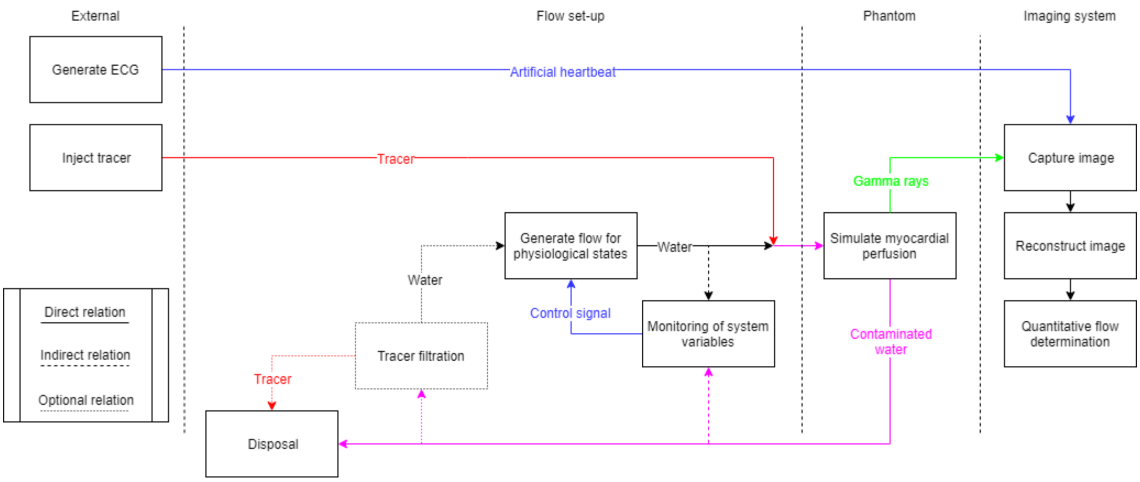

Figure 3.2: Overall block diagram

3.2 Function requirements

This section specifies the requirements set for the functions mentioned in figure 2.2.

3.2.1 Generate flow

In the project plan, a literature overview is given on perfusion phantoms, for a variety of organs, but also on physiological factors: perfusion rates, blood pressures, rates of stenosis et cetera. The TFR-GF requirements are based on the estimates by Uren et al. (1994), summarised in appendix A, Chiribiri et al. (2013), Ho et al. (2014), summarised in appendix B, and Slart (2015).

Decisions and design choices are given in table 3.1, quantitative requirements are given in table 3.2.

Table 3.1: Textual requirements for function: Generate flow

Requirement number	Description
TFR-GFT01	A variable, but constant, flow is to be generated, i.e. non-pulsatile.
TFR-GFT02	Flow generators need to be interchangeable.
TFR-GFT03	Flow feedback control for flow generators.

TFR-GFT01 is based on reducing the complexity of the set-up. The ROI based AIF averages the intensity over time, which removes the pulsatile nature. Furthermore, the heart rate cannot be determine in the measurements results. Therefore, pulsatile flow is not a priority. **TFR-GFT02** is based on maintaining flexibility such that the most optimal flow generator can be chosen based on the requirements for a specific experiment.

TFR-GFT03 is based on ensuring reliability; no validation can be performed when the flow is not controlled.

Table 3.2: Quantitative requirements for function: Generate flow

Requirement number	Description		Value	Unit
TFR-GFQ01*	Upper limit myocardial perfusion.	=	300	mL/min/100g
TFR-GFQ02*	Lower limit myocardial perfusion.	=	60	mL/min/100g
TFR-GFQ03*	Typical perfusion rate during stress.	> | <	190 | 300	mL/min/100g
TFR-GFQ04*	Typical perfusion rate during rest.	> | <	60 | 95	mL/min/100g
TFR-GFQ05**	Upper limit cardiac output.	=	8	L/min
TFR-GFQ06+	Lower limit arterial pressure.	=	56	mmHg
TFR-GFQ07+	Upper limit arterial pressure.	=	155	mmHg
TFR-GFQ08	Mean Arterial Pressure (MAP)[1].	=	89	mmHg
TFR-GFQ09	Typical MAP.	> | <	70 | 110	mmHg
TFR-GFQ10	Feedback control accuracy	=	5	%

** combined flow to myocardium, indicated by blue arrows in figure 3.3.*
*** flow **not** entering the myocardium, indicated by red arrow in figure 3.3.*
+ based on diastolic and systolic blood pressures, respectively. Measured at dashed line P in figure 3.3.

3.2.2 Measuring flow and pressure

This section focusses on the requirements for the measuring of the system variables; flow and pressure.

[1] Calculated as: $MAP \simeq DP + {}^1/_3(SP - DP)$

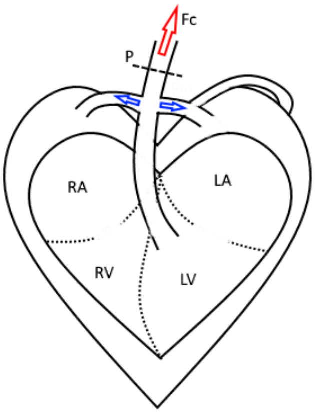

Figure 3.3: Simplified, schematic overview of the heart.

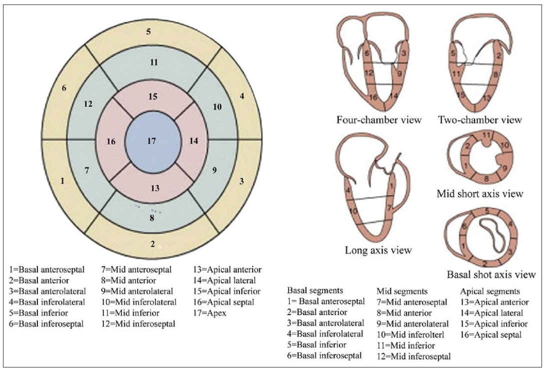

Figure 3.4: 17-segment heart model

Table 3.3: Quantitative requirements for function: Measure flow and pressure

Requirement number	Description		Value	Unit
TFR-MFPQ01	Flow measuring accuracy.	<=	5	%
TFR-MFPQ02	Pressure measuring accuracy.	<=	5	%
TFR-MFPQ03	Absolute flow resolution.	>=	1	mL/min
TFR-MFPQ04	Sampling rate.	>=	10	Hz

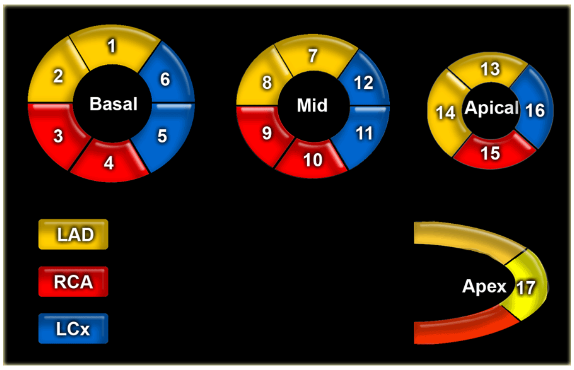

Figure 3.5: Schematic representation of the supply to each segment (simplified).

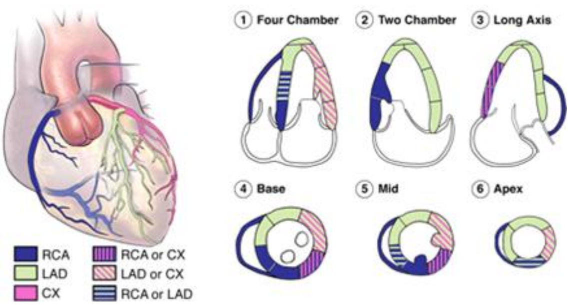

Figure 3.6: Schematic representation of the supply to each segment.

3.2.3 Simulate myocardial perfusion

This section specifies the requirements specified for the simulation of the myocardium.

Table 3.4: Function requirements for function: Simulate myocardial perfusion

Requirement number	Description
~~TFR-SIMT01~~	~~An AIF must be extractable from the left ventricle, as per software requirement.~~
TFR-SIM02	Stenotic arteries are mimicked in a physiological way by physically narrowing (or increasing flow resistance) of certain arteries.
TFR-SIMT03	Different stenotic severity, should be possible by, for example, variable flow resistors or interchanging components.
TFR-SIMT04	The phantom must be compatible with D-SPECT protocol.
A)	Flow to the myocardium is supplied by the RCA, LAD, and LCx.
B)	Flow for each segment is supplied individually by branches of the RCA, LAD, and LCx, see figure 3.5.
C)	Flow from each segment is measured separately such that they can be compared to the 17-segment model.
D)	An ROI for the AIF can be taken in the left atrium. Alternatively, the ROI for the AIF can be taken in the left ventricle.
~~E)~~	~~An AIF can be taken from the left atrium.~~
F)	The left ventricle's myocardium has a Vertical and Horizontal Longitudinal Axial (VLA/HLA) cross-sectional shape of a horseshoe.
G)	The left ventricle's myocardium has a Short Axial (SA) cross-sectional shape of a circle.
H)	The phantom is oriented such that it mimics a patient in supine position.
TFR-SIMT05*	Phantom's compartment model should match the currently practised protocol.
A)	The tracer specified in section 3.2.4.
B)	The contrast agent is absorbed by the myocardium to approximately 1.2% of administered activity in 5 minutes.
C)	Contrast accumulates in skeletal muscles, spleen, liver, and kidneys (potential interference).

*https://pubchem.ncbi.nlm.nih.gov/compound/131704316#section=Absorption-Distribution-and-Excretion

TFR-SIMT02 is based on the assumption that the relation between arteries, especially when some are narrowed, is too complex to be modelled independently. Simply reducing the overall flow in the myocardium will not capture that relation. Each segment of the left ventricle is supplied by a different branch of the three coronary arteries. One narrowed branch will have an impact on *all* other branches, which leads to **TFR-SIMT03**. The severity of the stenosis will impact the other branches differently.

TFR-SIMT04 is based on the goal of the project; to validate the D-SPECT. As mentioned in section 2.2.1, the relatively less expensive, less invasive (patient friendliness and dose reduction), faster and more accurate system makes it suitable for myocardial perfusion imaging. However, the quantitative nature of the dynamic scanning protocol requires validation since it has not been carried out. Furthermore, the learning, educational, and training purposes of the phantom study is desired by researchers, manufacturers, and medical personnel. This is somewhat extended by **TFR-SIMT05**. Protocols already exist within clinics and is therefore the best starting point for research and phantom development.

3.2.4 Inject tracer

The injection of tracer into the flow set-up, is carried out by an external infusion pump.

Table 3.5: Textual requirements for function: Inject tracer

Requirement number	Description
TFR-ICT01	Tracer volume is variable.
TFR-ICT02	Tracer activity is variable, also see TFR-ICQ03.
TFR-ICT03	Tracer agent is variable.
TFR-ICT04	Tracer injection is reproducible, also see TFR-ICT05.
TFR-ICT05	Tracer protocol should match the currently practised protocol.
A)	See TFR-ICQ01.
~~B)~~	~~Tracer is injected, as bolus, via infusion pump.~~
C)	A pre-bolus is to precede the main bolus.

TFR-ICT01 through **TFR-ICT03** are defined such that the tracer protocol can be optimised by performing experiments with different volumes, activity, or tracers. However, the first experiments will focus on the currently practised protocol, as is stated in **TFR-ICT05**. **TFR-ICT04** is based on the first experiments performed at the ZGT, Hengelo, where it is concluded that manual injection is not reproducible and results in unreliable results. These effect are directly visible in the dynamic scans. Therefore, an infusion pump is to be used.

Table 3.6: Quantitative requirements for function: Inject tracer

Requirement number	Description		Value	Unit
TFR-ICQ01	Tracer to be used.	=	Technetium Tetrofosmin	(^{99m}Tc)
TFR-ICQ02	Pre-bolus activity.	=	37	Mega Becquerel
TFR-ICQ03*	Typical main bolus activity.	> | <	500 | 700	Mega Becquerel
TFR-ICQ04+	Typical main bolus volume.	> | <	1 | 2	Millilitre
TFR-ICQ05+	Typical main bolus injection speed.	> | <	1 | 2	Millilitre per second
TFR-ICQ06+	Saline flush after tracer injection.	=	30	Millilitre

** hefty patient tend to get higher activity injected, i.e. 700 MBq.*
+ based on D-SPECT manufacturer's specification and current clinical protocol.

3.3 Physical requirements

[inpr] Determine size of seating of D-SPECT

[done] Determine weight limit of seating of D-SPECT

[todo] Must it be completely anatomical? Discuss with Kees

[todo] Adjust requirements if the phantom does not have to be anatomical.

This sections specifies the requirements on the physical aspects of the phantom and flow set-up, a.o. sizes, dimensions.

Table 3.7: Physical requirements (textual)

Requirement number	**Description**
TR-PRT01	The phantom's left ventricle is to be placed inside the QRM TRX-116, see TR-PRQ01.
TR-PRT02	The phantom's left ventricle must fit in the D-SPECT's imaging area.
TR-PRT03	The phantom must be anatomically shaped.
~~A)~~	~~In correspondence with requirements TFR-SIMT04.~~
B)	Four chambered phantom that correspond to left/right ventricle and left/right atrium.
C)	Segmented myocardium surrounds heart chambers.
~~D)~~	~~Three coronary arteries, RCA, LAD and LCx, supply the myocardium.~~
E)	The coronary arteries run outside of the myocardium.
F)	The coronary veins run outside of the myocardium.
TR-PRT04	The flow set-up is to remain horizontal (preventing additional flow resistance).
TR-PRT05	The phantom cannot contain air bubbles.

[todo] Why only left ventricle?

TR-PRT01 is based on creating realistic simulation of myocardial perfusion, thereby requiring a thorax phantom (with possible extension rings to simulate more hefty patients). The QRM TRX-116 has been successfully used for CT experiments. The 4DM software looks at the left ventricle thereby requiring the left ventricle to be in the phantom and in the imaging area, as stated in **TR-PRT02**.

[todo] Must it be anatomically shaped?

TR-PRT04 is based on the choice to prevent unnecessary complexity. Remaining horizontal will negate gravity.

TR-PRT05 is based on the attenuation of air, which compromises the TAC determination.

Table 3.8: Physical requirements (Quantitative)

Requirement number	**Description**		**Value**	**Unit**
TR-PRQ01	Short Axial diameter.	<	100	Millimetre
TR-PRQ02	Weight on patient chair.	<	171	Kilogram
TR-PRQ03+	Phantom's outer dimensions.			
A)	Basal-Apical distance.	≈	120	Millimetre
B)	Left-Right Lateral distance.	≈	80	Millimetre
C)	Anterior-Posterior distance.	≈	60	Millimetre
TR-PRQ04++	Left ventricle dimensions.			
A)*	Internal Apical-Annular distance.	> | <	69.4 | 105.8	Millimetre
B)	Internal Septal-Lateral distance.	> | <	38.2 | 55.6	Millimetre
C)	Internal Anterior-Inferior.	> | <	46.9 | 68.5	Millimetre
D)	Myocardial wall thickness.	> | <	4.8 | 9.8	Millimetre
E)=	Internal volume.	> | <	47 | 156	Millilitre
TR-PRQ05++	Right ventricle dimensions.			
A)	Internal Apical-Annular distance.	> | <	44.8 | 79.2	Millimetre
B)	Internal Septal-Medial distance.	> | <	19.2 | 40.0	Millimetre
C)	Internal Anterior-Inferior distance.	> | <	42.2 | 73.6	Millimetre
D)	Myocardial wall thickness.	> | <	1.0 | 3.8	Millimetre
E)=	Internal volume.	> | <	24.9 | 163.0	Millilitre
TR-PRQ06+	Phantom resembles weight of average human heart.	> | <	250 | 350	Gram
TR-PRQ07	Flow path height relative to platform (see figure 3.7 and 3.8).			
A)	Without extension rings.	≈	120 ± 10	Millimetre
B)	With extension ring M.	≈	145 ± 10	Millimetre
C)	With extension ring L.	≈	170 ± 10	Millimetre
D)	With extension ring XL.	≈	245 ± 10	Millimetre

** Annular → Annulus → assuming mitral valve level.*
+ based on OpenStax College (2013).
++ based on Lin et al. (2008).
= based on Maceira et al. (2006a) and Maceira et al. (2006b)

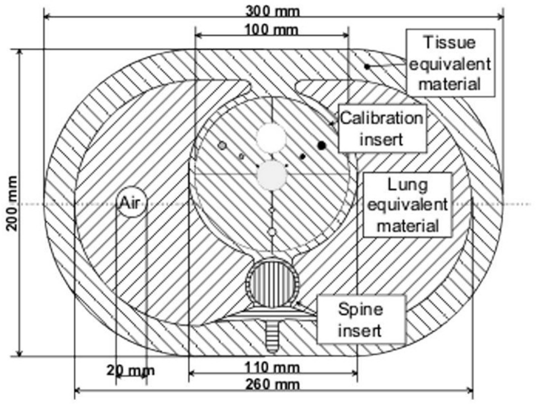

Figure 3.7: QRM thorax phantom.

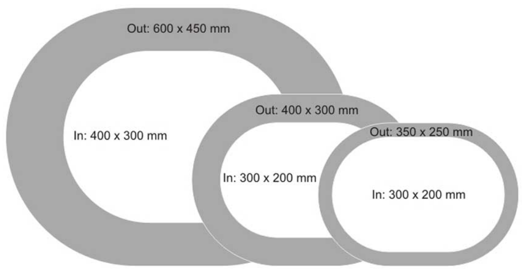

Figure 3.8: QRM thorax phantom extension rings.

3.4 External requirements

[todo] Determine how much noise output it may have.

[done] Determine the height of the chair of the D-SPECT

This section specifies the requirements that result from external influences.

Table 3.9: External requirements (Textual)

Requirement number	Description
TR-ERT01	No high-density or "High-Z" material is to be used.
TR-ERT02	The phantom's left and front side must remain free, see figure 3.9.
~~TR-ERT03**~~	~~Any part of the flow set-up and/or phantom, that does not fit directly on the patient chair, must remain horizontal with the remaining parts between 63 and 93cm.~~

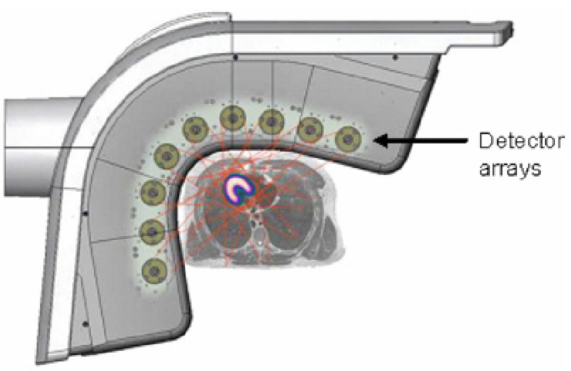

Figure 3.9: figure
Schematic drawing of D-SPECT head(Erlandsson et al., 2009).

TR-ERT01 is based on material properties; "High-Z", or High-Density, material tend to block gamma radiation emitted by SPECT tracers. Some examples of High-Z materials are Titanium (Ti), Chromium (Cr), Vanadium (V), Iron (Fe), or Lead (Pb).

TR-ERT02 is based on the D-SPECTS design. The curved design allows for better patient comfort and proper imaging, but will require the phantom for being accessible, i.e. not blocked by High-Z materials, from the patient's left and front side.

Table 3.10: External requirements (Quantitative)

Requirement number	Description		Value	Unit
TR-ERQ01*	Electric power.			
A)	Supply voltage.	=	230	Volt
B)	Supply current at TR-ERQ01 A).	< <	6	Ampere
C)	Supply type.	=	AC	-
C2)	Supply frequency	=	50	Hertz

** electric power connection (wall socket) for all systems, standard Dutch power mains.* ***No more than TR-ERQ01 B) can be drawn due to hospital safety measures.***

3.5 External interfaces

This section specifies the requirements for the external interface, between user and set-up.

Table 3.11: External interface requirements (textual)

Requirement number	Description
TR-EIT01	Adjust output of flow generators.
TR-EIT02	Serial communication between control/monitoring systems and external interface.

TR-EIT01 is based on the different experiments that need to be performed at different flow rates to determine the effect on the outcome.

TR-EIT02 is based on the current control and monitoring system, which is connected via USB to the external interface running on in MATLAB on a laptop.

Table 3.12: External interface requirements (Quantitative)

Requirement number	Description		Value	Unit
TR-EIQ01	Live plotting frequency of system's flow and pressure.	=	10	Hertz

3.6 System qualities

[todo] Specify pressure threshold.

This section specifies additional requirements that define the system's quality.

Table 3.13: System qualities

Requirement number	Description
TR-SQT01	Emergency shut down of flow set-up when arterial pressure exceeds TFR-GFQ07.
TR-SQT02	Emergency shut down of flow set-up when flow cannot be controlled, i.e. erratic or absent.
TR-SQT03	No reversed flow out of the phantom is allowed.

TR-SQT01 and **TR-SQT02** are based on safety and prevention of leakage. Excessive pressure indicates faulty situation which must be resolved before components fail. Erratic, and especially the absence of proper flow, indicates a leakage and must be resolved. Leakage after injecting the tracer must be prevented at all costs.

TR-QRT03 is based on optimisation of the experiments. Once the phantom is filled, it must remain filled such that experiments can be performed quickly in succession.

3.7 Constraints and Assumptions

This section specifies the design constrains that have been imposed and the assumptions that have been made.

Table 3.14

Reference number	Description
TR-CAT01	Beating artefacts will not be generated.
TR-CAT02	Breathing artefacts will not be generated.
TR-CAT03	Hefty patients are simulated using extension rings on the thorax phantom.

TR-CAT01 and **TR-CAT02** are set to prevent over-complicating the first myocardial perfusion phantom. Breathing artefacts may be generated by means of a breathing thorax phantom, which is being developed in Münster, Germany. However, it will make the first phantom too complex. There is potential for the breathing phantom in the second iteration.

Extension rings can be used for the static thorax phantom, see TR-PRT01. These extension rings can increase the amount of "tissue" between the heart phantom (placed in the center) and the scanner. This will simulate more hefty patients, as stated by **TR-CAT03**.

A Appendix: Normal heart rate/blood pressure and myocardial perfusion rates by Uren et al. (1994)

The following tables summarise Uren et al. (1994).

Table A.1: Heart rate and blood pressure according to Uren et al. (1994).

This table shows the heart rate and blood pressure in (Uren et al., 1994) among 35 patients with single-vessel CAD and 21 control patients.

		Control	**Stenosis**
Heart rate [BPM]	Base line	65 ± 7	63 ± 10
	MV*	84 ± 10	88 ± 16
Blood pressure [mmHg]	Diastolic (B)	76 ± 8	74 ± 11
	Diastolic (MV)	75 ± 12	72 ± 12
	Systolic (B)	132 ± 19	148 ± 22
	Systolic (MV)	140 ± 20	153 ± 21

** Maximal Vasodilation (MV)*

Table A.2: Myocardial blood flow according to Uren et al. (1994).

This table shows the determined perfusion rates in (Uren et al., 1994), converted to ml/min/100g.

	Control	**Stenosis**			
		<40%	40-59 %	60-79%	>80%
Base line	113 ± 26	96 ± 19	125 ± 34	123 ± 57	92 ± 33
MV*	337 ± 125	344 ± 147	207 ± 83	151 ± 37	122 ± 36

** Maximal Vasodilation (MV)*

B Appendix: Normal heart rate/blood pressure and myocardial perfusion rates by Ho et al. (2014)

The following tables summarise Ho et al. (2014).

Table B.1: Heart rate and blood pressure according to Ho et al. (2014).

This table shows the heart rate and blood pressure in (Ho et al., 2014) among 35 patients with documented CAD and 35 control (low-risk) patients. The 35 documented CAD patients are from a previous study.

		Control	**Stenosis**
Heart rate [BPM]	Base line	66 ± 10	73 ± 14
	MV*	88.54 ± 11.45	82 ± 16
Blood pressure [mmHg]	Diastolic (B)	63 ± 13	–
	Diastolic (MV)	56 ± 10	–
	Systolic (B)	111 ± 17	–
	Systolic (MV)	105 ± 21	–

** Maximal Vasodilation (MV)*

Table B.2: Myocardial blood flow according to Ho et al. (2014).

This table shows the myocardial perfusion rates by Ho et al. (2014), given in mL/min/100g.

	Low risk	**Historic ischaemia**	**Previous infarction**
Global rest	74.08 ± 16.3	82.29 ± 16.87	81.98 ± 18.54
Global stress	141.92 ± 30.83	107.95 ± 25.25	106.93 ± 32.91

C Appendix: heart chamber volumes by Lin et al. (2008)

The following tables summarise Lin et al. (2008) who investigated the ventricles and atria of 103 non-obese adults using 1D, 2D, and 3D techniques.

Table C.1: Heart chamber volumes according to Lin et al. (2008).

		End-systolic volume [mL]	**End-diastolic volume** [mL]	**Average wall thickness** [mm]
LV	2D	65.2 ± 20.9	150 ± 35.6	7.3 ± 1.3
	3D	52.6 ± 19.2	143.6 ± 36.4	
RV	2D	–	–	2.4 ± 0.7
	3D	82.10 ± 29.2	174.9 ± 48.0	
LA	2D	86.5 ± 29.1	-	–
	3D	102.3 ± 24.4	–	
RA	2D	–	–	–
	3D	111.9 ± 29.1	–	

Left Ventricle (LV), Right Ventricle (RV), Left Atrium (LA), Right Atrium (RA)

Table C.2: Heart chamber sizes according to Lin et al. (2008).

LV [mm]			**RV** [mm]		
	End-Systolic	End-Diastolic		End-Systolic	End-Diastolic
SL	–	47.4 ± 4.7	SM	29.6 ± 5.3	37.0 ± 5.7
AI	–	57.7 ± 5.5	AI	29.6 ± 5.3	72.6 ± 9.0
AA	–	87.6 ± 9.3	AA	62.0 ± 8.8	77.7 ± 10.4

Left Ventricle (LV), Right Ventricle (RV), Septal-Lateral (SL), Anterior-Inferior (AI), Apical-Annular (AA), Septal-Medial (SM)

D Appendix: heart chamber volumes by Maceira et al. (2006a,b)

The following table summarises Maceira et al. (2006a,b), who investigated the left and right ventricles, respectively, of 120 patients.

Table D.1: Heart chamber volumes according to Lin et al. (2008).

		End-systolic volume [mL]	**End-diastolic volume** [mL]
LV	All	47 ± 10	142 ± 21
	Female	42 ± 9.5	128 ± 21
	Male	53 ± 11	156 ± 21
RV	All	50 ± 14	144 ± 23
	Female	43 ± 13	126 ± 21
	Male	57 ± 15	163 ± 25

Left Ventricle (LV), Right Ventricle (RV), Left Atrium (LA), Right Atrium (RA)

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