Partial volume and motion correction in cardiac PET: first results from an *in* vs *ex vivo* comparison using animal datasets.

A. Turco, PhD^{a,c}, O. Gheysens, MD, PhD^{a,b}, J. Duchenne, MSc^c, J. Nuyts, PhD^a, F. Rega, MD, PhD^{c,d}, J.U. Voigt, MD, PhD^{c,e}, K. Vunckx, PhD^a, P. Claus, PhD^c

^a*KU Leuven - University of Leuven, Department of Imaging and Pathology, Nuclear Medicine and Molecular imaging, Medical Imaging Research Center (MIRC), B-3000 Leuven, Belgium.*

^b*University Hospitals Leuven, Department of Nuclear Medicine, B-3000 Leuven, Belgium.*

^c*KU Leuven - University of Leuven, Department of Cardiovascular Sciences, Medical Imaging Research Center (MIRC), B-3000 Leuven, Belgium.*

^d*University Hospitals Leuven, Department of Cardiac Surgery, B-3000 Leuven, Belgium.*

^e*University Hospitals Leuven, Department of Cardiovascular Diseases, B-3000 Leuven, Belgium.*

Abstract

Background. In a previous study on *ex vivo*, static cardiac datasets, we investigated the benefits of performing partial volume correction (PVC) in cardiac ¹⁸F-Fluorodeoxyglucose(FDG) PET datasets. In the present study, we extend the analysis to *in vivo* cardiac datasets, **with the aim of defining which reconstruction technique maximises quantitative accuracy and, ultimately, makes PET a better diagnostic tool for cardiac pathologies.**

Methods. *In vivo* sheep datasets were acquired and reconstructed with/without motion correction and using several reconstruction algorithms (with/without resolution modelling, with/without non-anatomical priors). Corresponding *ex vivo* scans of the excised sheep hearts were performed on a small-animal PET scanner (Siemens Focus 220, microPET) to provide high-resolution reference data unaffected by respiratory and cardiac motion. A comparison between the *in vivo* cardiac reconstructions and the corresponding *ex vivo* ground truth was performed.

Results. The use of an edge-preserving prior (Total Variation (TV) prior in this work) in combination with motion correction reduces the bias in absolute quantification when compared to the standard clinical reconstructions (-0.83 vs -3.74 SUV units), when the end-systolic gate is considered. At end diastole, motion correction improves absolute quantification but the PVC with priors does not improve the similarity to the ground truth more than a regular iterative reconstruction with motion correction and without priors. Relative quantification was not influenced much by the chosen reconstruction algorithm.

Conclusions. The relative ranking of the algorithms suggests superiority of the PVC reconstructions with dual gating in terms of overall absolute quantification and noise properties. **A well-tuned edge-preserving prior, such as TV, enhances the noise properties of the resulting images of the heart. The end-systolic gate yields the most accurate quantification of cardiac datasets.**

Keywords: cardiac PET, motion correction, partial volume correction, quantification

List of abbreviations

^{18}F -FDG ...	^{18}F -Fluorodeoxyglucose
PET	Positron Emission Tomography
PVE	Partial Volume Effect
PVC	Partial Volume Correction
OSEM	Ordered Subsets Expectation Maximisation (reconstruction algorithm)
RR	Resolution Recovery
MAP	Maximum-a-Posteriori (reconstruction algorithm)
TV	Total Variation (prior)
SUV	Standard Uptake Values
LV	Left Ventricular

1. Introduction

The characterization of cardiac pathologies by means of positron emission tomography (PET) is progressively increasing [1]. In recent years, it has been hypothesised that hemodynamic or mechanical indicators of the cardiac workload collected from a patient (e.g. left-ventricular (LV) pressure

6 and/or myocardial deformation) can be correlated to specific uptake patterns
7 of ^{18}F -FDG [2]. If such correlation was proven, PET images could have the
8 potential to offer, in a non-invasive fashion, parameters useful to improve the
9 assessment of the progression and the severity of cardiac pathologies. Addi-
10 tionally, it could better predict the responsiveness of patients to the planned
11 therapeutic program (e.g. cardiac resynchronization therapy).

12 Regional differences in myocardial ^{18}F -FDG uptake have been observed
13 in the past [3]. However, a regionally inhomogeneous wall thickness in re-
14 modelled hearts might cause an apparently different uptake within the re-
15 constructed heart images due to the limited spatial resolution of the PET
16 system. In a recent study [4], we investigated the necessity of partial volume
17 correction (PVC) techniques during reconstruction of cardiac datasets in a
18 simplified scenario where no motion affected the datasets. **In that study, the**
19 **partial volume correction performance of iterative image reconstruction with**
20 **resolution modelling and edge-preserving priors was evaluated. We consid-**
21 **ered both priors based on anatomical side-information (e.g. from computed**
22 **tomography) and non-anatomical priors that favour piecewise smoothness**
23 **(e.g. the total variation (TV) prior[5]).** The use of such non-anatomical pri-
24 ors had shown to improve the absolute quantification of the LV myocardium
25 of the available datasets, when compared to the state-of-the-art iterative
26 reconstruction algorithms (with or without resolution recovery).

27 In addition, the motion of the heart during the entire PET examination
28 – due to the heartbeat and to the breathing motion to which the heart is
29 indirectly subject – causes additional uncertainty on the estimated tracer
30 distribution. Several studies have highlighted the usefulness of motion cor-
31 rection techniques for the improved reconstruction of cardiac datasets [6, 7].
32 However, the comparison of the obtained, motion-corrected datasets against
33 a ground truth has not been performed yet. All previous studies perform
34 a comparison between motion-corrected and static reconstructions, and re-
35 port the improvements based on changes in specific indicators such as wall
36 thickness, ejection fraction or cavity volume [8, 9].

37 To our knowledge, the combination of motion-correction and partial vol-
38 ume correction techniques for the reconstruction of cardiac datasets acquired
39 on a clinical PET/CT scanner has not been thoroughly evaluated. The aim
40 of this work is to utilise the available *in* and *ex vivo* animal datasets to
41 investigate this issue.

2. Methods

Thirteen Swifter x Charolais cross-breed female sheep with body weight 38 ± 3 kg were used for these experiments and subjected to the same pacing and imaging procedure. Each animal had a pacemaker implanted, which was set to pace the heart at 180 beats per minute during 8 weeks to achieve dilated cardiomyopathy with asymmetric remodelling of the LV walls [10]. It was expected that different parts of such remodelled hearts would be affected differently by the partial volume effect (PVE) (e.g., the thinner septum was expected to be more affected by blurring, when compared to the lateral wall) and that therefore, PVC would have a significant effect on the tracer uptake analysis.

At 8 weeks, the remodelling of the heart reached a plateau and the imaging protocol was started. For all imaging procedures and measurements, the pacemaker of the sheep was set to a fixed heart rate of 110 beats per minute. The animals were anaesthetised with isoflurane and mechanically ventilated with an endotracheal tube during all experimental procedures.

All procedures performed in this study involving animals were in accordance with the ethical standards of our institution (project number P146/2012) and complied with the European Commission Directive 2010/63/EU.

Acquisition of the animal datasets

Each of the animals went through euglycemic-hyperinsulinemic clamping to maximize glucose uptake in the heart [11]. Once steady-state was achieved, each sheep was injected with ^{18}F -FDG and a PET scan of 30 minutes was performed (*in vivo* scan) 30 minutes post-injection on a clinical PET/CT scanner (Siemens Biograph 16, Hirez). The mean activity at the beginning of the *in vivo* scans was 310.5 (range: 109-477) MBq. During this scan, the respiratory and cardiac motion of the animals were recorded with an Anzai AZ773V respiratory belt and an ECG tracking device, to enable off-line motion correction of the *in vivo* datasets. An attenuation correction (AC) CT was acquired in a fixed cardiac and respiratory phase. This was achieved by disconnecting the endotracheal tube for the duration of the AC CT and by retrospectively gating the acquired CT for cardiac motion. Another AC CT was obtained in a fixed respiratory phase, using the same procedure as above, and no cardiac gating. After the scan, each sheep was sacrificed under isoflurane anaesthesia with intravenous 160 mg/kg pentobarbital and 50 ml of saturated KCl. The mean time elapsed between the end of the *in vivo* scan

78 and the sacrifice, calculated on 8 sheep datasets for which the approximate
79 sacrifice time was available, was 21 minutes (min:15/max:32 minutes). The
80 heart of each sheep was explanted immediately after sacrifice. Each heart was
81 filled with a low-attenuating, hardening polyurethane foam. Once the foam
82 was solid, a 15-minute PET scan on a small-animal PET scanner (Siemens
83 Focus220 microPET) was performed, followed by a 10-minutes transmission
84 scan for scatter correction and a 20-minutes PET scan of the same heart on
85 the clinical PET/CT Hirez scanner. A high-dose, high-resolution (HR)CT
86 was also acquired on the clinical PET/CT scanner for each of the *ex vivo*
87 hearts. It was used both for attenuation correction (AC) and as anatomical
88 information for both the microPET and the Hirez *ex vivo* datasets.

89 ***Motion correction of the in vivo datasets***

90 The acquired *in vivo* animal PET datasets were either not corrected for
91 motion (*static* datasets), or corrected for motion using a phase-based gating
92 approach [12]. This approach was chosen to be consistent with the algorithm
93 used by the scanner and was supported by the regularity of the breathing
94 cycles. In the latter case, the initial dataset was split into 5 respiratory gates.
95 The gate containing data corresponding to end-expiration was subsequently
96 split into 10 cardiac gates. Each of the resulting gates contained the events
97 collected in one particular cardiac and respiratory phase. Due to the very low
98 amount of data resulting from the dual-gating of the *in vivo* datasets, two of
99 the sheep datasets could not be considered for the subsequent analysis.

100 ***Reconstruction of the datasets***

101 *Ex vivo, ground-truth datasets*

102 The purpose of this study was to compare the output of different correc-
103 tion methods to a ground-truth dataset, which was here represented by the *ex*
104 *vivo* microPET datasets. Iterative reconstructions of the microPET images
105 were performed as in [4](5 iterations $\times$ 28 subsets). These included resolu-
106 tion recovery and the application of an anatomy-based prior (asymmetrical
107 Bowsheer prior, $w = 50$, $n = 9$). A prior was applied because resolution re-
108 covery alone is known to reduce the apparent thickness of the structures and
109 to possibly hamper quantification [13]. Moreover, Bowsheer reconstructions
110 have been shown to improve the recovery of activity concentrations [14].

111 *Static in vivo reconstructions*

112 The **static** reconstructions were obtained using in-house developed soft-
 113 ware which attempted to reproduce as closely as possible a typical clinical re-
 114 construction. 3D reconstructions using an iterative algorithm (ordered-subsets
 115 expectation-maximisation, OSEM) were computed, using a ray-tracing pro-
 116 jection without resolution modelling. The voxel size was set to 2.66×2.66
 117 $\times 2$ mm and 4 iterations $\times$ 8 subsets were chosen.

118 *Gated in vivo reconstructions*

119 The algorithms that were used to reconstruct the **dual-gated** datasets
 120 were chosen based on our previous study on PVC of the *ex vivo* datasets [4]:

- 121 • a 3D OSEM reconstruction with resolution recovery (RR): OSEM+RR.
- 122 • an iterative reconstruction algorithm with prior information (maximum
 123 a-posteriori, MAP) with RR: MAP-RR+TV. The prior information mit-
 124 igates the artefacts produced by resolution modelling alone, and the
 125 noise that affect the reconstructions [5]. The MAP-RR+TV recon-
 126 structions were performed using a weight (β) of 0.005 for the prior,
 127 which defines its strength. This value was chosen based on a previous
 128 optimisation study, where it proved to produce clinically acceptable
 129 images with improved noise properties [15]. Additionally, we verified
 130 that such choice yielded visually acceptable reconstructions also for the
 131 current datasets.

132 In-house developed software was used to perform the reconstruction of
 133 all the dual-gated datasets. A distance-driven projection method was used
 134 to ensure that all voxels are well sampled during the reconstruction [16].
 135 These projectors are being recently integrated into clinical PET systems
 136 thanks to their favourable numerical characteristics. A resolution recovery
 137 (RR) technique is however needed to account for the finite spatial resolution
 138 of the PET system. The RR was achieved by sinogram smoothing with a
 139 Gaussian function (full width at half-maximum (FWHM) = 4.3/4.5 mm in
 140 the transaxial and axial directions, respectively).

141 In both the in-vivo and ex-vivo scans, the heart was positioned near the
 142 center of the field of view, where the resolution can be treated as shift-
 143 invariant with good approximation [17]. Hence, a spatially invariant resolu-
 144 tion modelling approach was used as a best compromise between construc-
 145 tion time and image quality.

146 The voxel size of the reconstructed PET images was set to 1.35^3 mm^3 .
147 The iteration scheme consisted of 3i42s (i: iterations, s: subsets), followed
148 by 2i24s and 2i1s.

149 *Dynamic in vivo reconstructions*

150 Our study analyses ^{18}F -FDG PET reconstructions obtained from datasets
151 acquired either 30 minutes post-injection (*in vivo* datasets) or after the sacri-
152 fice of the animal (*ex vivo* datasets), which in turn occurred about 1.5 hours
153 after tracer injection. Previous studies have documented a steady increase of
154 FDG tracer uptake in the LV wall up to 3 hours after patient injection [18].

155 Dynamic reconstructions of the available *in vivo* datasets were performed
156 to verify whether the datasets used in this study were affected by such grad-
157 ual increase of uptake. The original, ungated listmode was divided into 6
158 frames of equal length (5 minutes/frame). Each frame was individually re-
159 constructed using a distance-driven projection method, resolution modelling
160 in the sinogram space, the same iteration scheme as for the dual-gated recon-
161 structions and a voxel size of 2 mm in the three directions. Decay correction
162 of each of the dynamic frames was performed to the beginning of the *in vivo*
163 scan.

164 The breath-hold, cardiac-gated CT was used for the attenuation correc-
165 tion of all the aforementioned reconstructions. Scatter and randoms were
166 also modelled during the reconstruction of these datasets, using the scatter
167 and random estimates provided by third-party software (e7-tools, Siemens,
168 Knoxville).

169 *Image post-processing: polar maps (or bull's eye plots)*

170 17-segments polar maps (PMs) or bull's eye plots of the LV wall were
171 created according to the guidelines of the American Heart Association [19]
172 to evaluate the relative and absolute activity distributions in comparison to
173 the ground truth. The use of polar maps allowed to align the corresponding
174 LV regions of the *in vivo* and *ex vivo* reconstructions without the need for
175 a non-rigid registration between the two datasets. Additionally, polar maps
176 are a commonly used tool to assess the tracer uptake in nuclear medicine
177 studies.

178 *Max-count polar maps*

179 For each of the gated and static reconstructed datasets and for the ground
180 truth, the bull's eye plots were created as described in [20]. The delineation

181 of the LV wall was automatically performed by in-house software. Max-count
 182 polar maps were generated by taking the maximum value over the LV wall
 183 thickness at each radial and longitudinal position, within the automatically-
 184 defined endocardial and epicardial contours. A fixed distance of 1.6 cm was
 185 imposed between the endocardial and the epicardial contours, to fully en-
 186 compass the LV wall.

187 *Mean-count polar maps, total activity and scaling factor*

188 Mean-count polar maps were generated for all datasets (gated, static, dy-
 189 namic, ground-truth) by taking the mean value over the LV wall thickness
 190 at each radial and longitudinal position, within the automatically-defined
 191 endocardial and epicardial contours. A fixed distance of 1.6 cm was imposed
 192 between the endocardial and the epicardial contours, in order to fully en-
 193 compass the LV wall while excluding as much as possible the influence of
 194 the left-ventricular blood pool and of the right ventricle from the computa-
 195 tion of the total activity. Corresponding volumetric polar maps were also
 196 obtained, whose voxels indicate the volume of the corresponding section of
 197 the reconstruction. The multiplication and subsequent summation of all cor-
 198 responding voxels of the mean-count polar maps and the volumetric polar
 199 maps generated the **total LV wall activity** for each of the reconstructions.

200 The total LV wall activity for each of the 6 dynamic frames was plot-
 201 ted against time, for each animal, together with the total LV wall activity
 202 computed from the ground-truth dataset. The total activity at sacrifice time
 203 (measurement not available) was obtained by applying a logarithmic fit to
 204 the LV wall activity values computed on the dynamic frames. Such logarith-
 205 mic fit, which we expected would be representative of a biological process
 206 such as cardiac LV wall uptake, was performed to compare the sacrifice total
 207 LV wall activity value to the microPET value. This would thereby exclude
 208 any increases of activity between the sacrifice and the microPET scan. A
 209 paired t-test was performed between the extrapolated total activity at sacri-
 210 fice time and the computed total activity on the microPET reconstructions,
 211 to test the efficacy of the logarithmic estimation.

212 Each curve in Figure 1 shows the activity of the dynamic reconstruc-
 213 tions, the extrapolated activity at sacrifice time and the microPET activity
 214 for a specific sheep. The logarithmic fit was optimal for all animals (mean
 215 $R^2 > 0.95$). The extrapolated sacrifice value matches well with the calcu-
 216 lated total microPET activity (p-value of the paired t-test between the total
 217 extrapolated activity at sacrifice and the total microPET activity: $p = 0.24$

218 ≥ 0.05), thus confirming that the dynamic increase was most likely present
219 only during the portion of the experiment where the animal was alive.

220 Additionally, due to the fact that all the *in vivo* datasets (both gated
221 and ungated) contain data spanning over the 30 minutes, they all comprise a
222 portion of the dynamic activity increase (which is not corrected for). Thus,
223 their mean LV wall activity is always higher than the mean LV wall activity
224 at the beginning of the scan. As a consequence, the microPET LV wall
225 activity needs to be scaled to the activity of one of these reconstructions
226 (and not to the beginning of the scan). This would allow to compare the
227 absolute values of the microPET with those of the *in vivo* images of interest.
228 A **scaling factor** was therefore computed by dividing the total LV wall
229 activity of the static reconstruction of the *in vivo* data by the total LV
230 wall activity of the corresponding microPET reconstruction (*statscale*). The
231 static reconstruction was chosen as a reference in order not to bias the results
232 towards the dual-gated or partial-volume corrected reconstructions – which
233 are the subject of evaluation. The mean *statscale* factor computed over all
234 sheep was 0.84 ± 0.06 .

235 *Data analysis*

236 The max-count polar maps of corresponding *ex vivo* and *in vivo* datasets
237 were compared based on their absolute activity differences and on the relative
238 activity distribution.

239 For the **absolute** comparison, the scaling factor (as described in the pre-
240 vious section) was applied to the ground-truth datasets prior to any further
241 comparison. Bland-Altman plots were computed between the max-count po-
242 lar maps of the so-scaled ground-truth and all the *in vivo* reconstructions,
243 and the bias and limits of agreement were reported. The segments in the
244 Bland-Altman plots were color-coded based on the human vascular regions
245 to which they belong [19], in order to verify whether an increased or decreased
246 bias in any of these regions could be observed.

247 For the **relative** quantification, Bland-Altman plots were computed be-
248 tween the max-count polar maps of the ground truth and all the *in vivo*
249 reconstructions, both **normalized** to their respective maximum value, and
250 the bias and limits of agreement were reported as in [21]. By doing so, we
251 were able to globally highlight whether the differences in the relative myocar-
252 dial uptake were relevant or negligible. The analysis of the mean bias per
253 segment, over the entire animal cohort, allowed us to pinpoint if and which
254 (set of) segment(s) was particularly responsible for the observed differences.

Figure 1: Mean LV activity concentration in Standard Uptake Values (SUV) for all sheep datasets (one animal per color). The first 6 time points represent the total LV wall activity in the polar maps of each dynamic reconstruction of the *in vivo* dataset. The activity at sacrifice is extrapolated based on the logarithmic trendline that fit the dynamic points. The last point is the total LV wall activity computed from the polar map of the *ex vivo* (microPET) dataset. All reconstructions have been corrected for decay to the beginning of the *in vivo* scan before the computation of the activities.

Figure 2: The max-count polar maps are computed for each sheep and for each cardiac gate at end-expiration, and the mean of all these polar maps is then calculated (similarly to the procedure in [4]) and plotted in this graph. The mean value over all sheep is reported for each gate and for each algorithm. The microPET was here downscaled with the *statscale*. The OSEM3D reconstruction was post-smoothed with a Gaussian kernel of 5 mm (FWHM).

3. Results

Absolute quantification

A plot of the mean activity value in the whole heart, over all animals and for all 10 cardiac gates was obtained (Figure 2).

We can observe that the downscaled microPET lies in between the curves of the MAP-RR+TV and the OSEM3D+RR. The relative order of the algorithms (OSEM3D+RR is higher than the MAP-RR+TV, which is in turn higher than the uncorrected reconstructions) is similar to what was previously reported in previous studies on partial volume [4] and in agreement with what was expected with motion correction [22].

In Figure 3 and 4, the Bland-Altman plots for the static reconstructions and for the dual-gated, MAP-RR+TV and OSEM3D+RR reconstructions at two selected cardiac gates (end-systole and end-diastole) are reported. At end systole, we can appreciate a decrease in bias when the MAP-RR+TV reconstructions are used (-0.83 vs -3.74 when static reconstructions are used instead). A slight narrowing of the limits of agreement (4.31 for MAP-RR+TV vs 4.78 for the static reconstructions) can also be observed. Conversely, the OSEM3D+RR reconstructions show a positive bias of 2.99. This is to be expected, since these reconstructions are more noisy and are characterized by overshoots of activity, which produce an overestimation when compared to the microPET. The difference between MAP-RR+TV and OSEM3D+RR is almost as large as the limits of agreement for MAP-RR+TV, thus suggesting that the two methods are in global disagreement [23] – also considering the mean segmental values of the considered datasets, ranging between 8 and 18 SUV.

At end-diastole, a decrease in bias is observed when the OSEM3D+RR reconstructions are considered. Conversely, the bias that is obtained from the MAP-RR+TV reconstructions increases and becomes similar to that of the OSEM3D+RR in absolute values (-1.90 for MAP-RR+TV vs 1.64 for OSEM3D+RR). This can be explained by the fact that the MAP-RR+TV prior weight is not individually tuned for the various animals, thus possibly leading to greater smoothing in the (differently thinned) walls of the end-diastolic phase.

The MAP-RR+TV image is however superior in terms of noise properties when compared to the corresponding OSEM3D+RR reconstructions, as Figure 5 illustrates.

Figure 3: Bland-Altman (B-A) plots for the static (ungated), MAP-RR+TV (dual-gated) and OSEM3D+RR (dual-gated) reconstructions against the ground truth (microPET), at end-systole. Max-count polar maps were used to calculate the segmental values of both in- and ex- vivo datasets. The microPET was here scaled down using *statscale*. The segments are color-coded based on the vascular territory they belong to. (Red) LAD: left anterior descending artery segments, (Blue) RCA: right coronary artery segments, (Black) LCX: left circumflex artery segments. Dashed lines indicate the bias, dotted lines indicate the limits of agreement. Gray lines represent the global trend.

Figure 4: Bland-Altman (B-A) plots for the static (ungated), MAP-RR+TV(dual-gated) and OSEM3D+RR (dual-gated) reconstructions against the ground truth (microPET), at end-diastole.

Figure 5: OSEM3D+RR (left) and MAP-RR+TV (right) reconstructions at end-systole. Five different animals with increasing count levels from top to bottom. The MAP-RR+TV reconstructions appear smoother and better defined.

Relative quantification

The Bland-Altman plots obtained from the normalized max-count polar maps of the dual-gated MAP-RR+TV, OSEM3D+RR (end-systole) and the static reconstructions reveal very small differences compared to the ground truth (graphs not shown). The biases for all reconstruction and motion correction methods are below the 0.03 level, indicating an *overall* difference of less than 3% between the normalized polar maps of the in vivo datasets and the ground truth. The analysis of the bias *per segment* revealed a particularly negative bias for the segment 3 and 9 (-0.22 and -0.13, respectively) and a positive bias for segment 11 (+0.12), when the static reconstructions are considered. As for the dual-gated reconstructions, a particular bias is observed for segments 3 (-0.15 for MAP-RR+TV and -0.12 for OSEM3D+RR) and 17 (+0.12 for MAP-RR+TV and +0.11 for OSEM3D+RR). Figure 6 visually reports on the mean bias and standard deviation per segment, over the entire animal cohort, and allows us to visualize the aforementioned segments – i.e. those most responsible of the observed differences.

4. Discussion

PET is an important tool to assess myocardial perfusion and flow reserve, myocardial viability and has a great potential in emerging clinical applications such as quantification of tracer uptake in atherosclerotic plaques. Since PET images provide a multitude of information, quantitative measurements are important and allow to reduce observer variability. Therefore, the goal of this study was to optimize absolute quantification of myocardial tracer uptake compared to standard clinical reconstructions. We used 18F-FDG, a widely available tracer with relatively long half-life (109 min), which allowed us to perform both in vivo imaging and afterwards *ex vivo* imaging serving as reference unaffected by cardiac or respiratory motion. This would not have been possible with short-lived tracers (e.g. 11C-tracers or available perfusion tracers). The use of 18F-FDG is further supported by studies showing that FDG uptake is correlated with pressure-strain loop areas in patients with left bundle branch block, hence serving as a non-invasive measurement of myocardial work [2]. Another study comparing FDG and 18F-FTHA (fatty acid tracer) in patients with congestive heart failure demonstrated a shift in substrate metabolism which may be an indicator of impaired energy efficiency during heart failure[24]. This study correlates the tracer uptake in motion-corrected and static cardiac datasets to the tracer uptake of a scaled

Figure 6: Polar plots displaying the mean bias and the mean standard deviation of the differences obtained by subtracting the normalized *in vivo* reconstructions (top pane: static, middle pane:MAP-RR+TV, bottom pane: OSEM3D+RR) from the normalized microPET polar maps. Average values over all animals.

327 *ex vivo* ground truth, as a first attempt to pinpoint the optimal reconstruction
 328 method for absolute and relative quantification of cardiac datasets. Both
 329 cardiac and respiratory motion were corrected for in the considered *in vivo*
 330 datasets. In fact, it has been previously demonstrated that the combination
 331 of cardiac and respiratory motion correction leads to a more accurate
 332 estimation of myocardial uptake and a significant effect on resolution, and
 333 state-of-the-art motion correction methods nowadays aim at correction of
 334 both motions [25, 26, 27, 28].

335 In this work, we assumed that the intravascular activity in the myocardial
 336 wall is small compared to the trapped FDG and can be ignored with good
 337 approximation, because the *in-vivo* images are acquired between 30 and 60
 338 minutes after the injection.

339 The Bland-Altman plots report an improvement when motion correction
 340 is applied to the considered datasets. Additionally, the graph showing the
 341 mean activity computed on the max-count polar maps of the *in vivo* recon-
 342 structions shows a ranking that is similar to what was observed in a previous
 343 study on *ex vivo* datasets, where the OSEM3D+RR over-estimated the total
 344 activity and the MAP-RR+TV was the closest to the ground truth [4].
 345 This gives a first indication that the results previously obtained on *ex vivo*
 346 datasets can be transferred to the *in vivo* scenario.

347 The similarity to the ground truth is maximal for the end-systolic gate,
 348 which is the gate characterised by thicker walls and thus less prone to blur-
 349 ring due to PVE or to the suboptimal choice of the MAP-RR+TV weight and
 350 smoothing mask. A smaller bias was expected when the MAP-RR+TV prior
 351 and the end-diastolic gate were considered. In this latter case, a similar bias
 352 (absolute value) is observed for the MAP-RR+TV and the OSEM3D+RR
 353 reconstruction, thus questioning the necessity of the additional application
 354 of prior information. However, a more tailored tuning of the TV prior pa-
 355 rameters to the specific subject may reduce this bias. MAP-RR+TV images
 356 are anyway less noisy, and at worst as far from the ground truth as the
 357 OSEM3D+RR (in absolute value), for what absolute quantification is con-
 358 cerned.

359 A number of limitations are connected to the current experimental setup,
 360 which used the microPET datasets as ground truth for PVC and motion
 361 correction techniques.

362 In our previous work [4] we compared the images of the *ex-vivo* hearts ob-
 363 tained from the microPET and the Hirez scanner, and their differences and
 364 similarities were extensively described. In that study, we concluded that the

365 *ex vivo* reconstructions with the non-anatomical prior achieved very good
 366 similarity to the microPET images, hence we can exclude that the differences
 367 between *ex vivo* and *in vivo* datasets are due to differences in reconstruction
 368 algorithm and partial volume effects. Two remaining factors, i.e. attenuation
 369 correction and scatter correction, could however still have a contribution to
 370 the *in vivo* datasets. This is a limitation of the current experimental setup.
 371 An *in vivo* scan of the intact sheep after stopping the heart could have ex-
 372 cluded the interference of the motion and have an intermediate *in vivo* image
 373 to use as a reference. However this was impossible due to governing standard
 374 operating procedures that do not allow to sacrifice animals in the scanner
 375 room and animals had to be moved to a dedicated room at distance for sacri-
 376 fice. Hence, no scans could be performed during the time between the end of
 377 the *in vivo* scans and the sacrifice of the animal, and the microPET datasets
 378 were scanned about an hour after the end of the *in vivo* scans. During this
 379 time, the activity concentration kept on increasing. The reconstruction of the
 380 dynamic frames of the acquired *in vivo* datasets helped to estimate a trend
 381 of FDG uptake for the LV myocardium over time. The obtained curves, for
 382 each of the analysed animals, corroborated those of a previous study which
 383 observed increased FDG uptake up to 3 hours after tracer injection [18].

384 Therefore, a method to correlate the microPET and the *in vivo* absolute
 385 values was also proposed in this work, which downscaled the total activity of
 386 the LV wall of the microPET reconstructions to match the total reconstructed
 387 LV wall activity of the *in vivo* datasets. This was necessary to take into
 388 account the dynamic increase of the FDG uptake with time. The microPET
 389 was scaled using the total activity of the static reconstructions, in order
 390 not to bias the conclusions towards one of the algorithms we wanted to
 391 evaluate. Despite all efforts to calculate the scaling factor in a sensible way,
 392 we cannot exclude that the use of a scaling factor might have biased all
 393 results towards one or the other reconstruction algorithm. However, the
 394 ranking of the algorithms reflected what was reported in previous literature.
 395 Additionally, the absolute activity values obtained at end-systole confirm
 396 that the proposed scaling technique can represent a reasonable trade-off.
 397 Although this is a limitation of the current experimental setup, we believe
 398 that this is an accurate scale factor estimation, additionally confirmed by the
 399 fact that the scaled microPET LV wall activity is similar to the estimated
 400 LV wall activity at sacrifice time.

401 We additionally correlated the relative distribution of activity within the
 402 LV wall of the *in vivo* and the *ex vivo* datasets, to assess whether the re-

gional activity distribution would be affected by the different motion correction techniques. We observed that neither reconstruction method affected the activity distribution within the *in vivo* sheep hearts, nor improved the similarity to the ground-truth. This can be explained by the fact that, in the analysed sheep, a similar blurring affected both the septum and the lateral wall due to respiration, and the differences in wall thickness were not so pronounced to determine a stronger blurring on one or the other side of the LV wall due to the partial volume effect. The analysis of the Bland-Altman plots on the normalized polar maps confirmed such visual observation and an overall good similarity of the normalized *in vivo* polar maps to the ground truth. Some segments, in the infero-septal and infero-lateral portion of the LV wall, revealed bigger discrepancies in the activity distribution, when the *in vivo* and the *ex vivo* scans are compared. This may be caused by the different shape and size of the *ex vivo* and the *in vivo* datasets, which could affect the perfect alignment of corresponding structures. Additionally, the filling of the *ex vivo* hearts with the polyurethane foam might have stretched and possibly modified the relative activity distribution in some of the datasets. Another possible explanation of this change in activity distribution is that the sacrifice of the sheep using KCl caused a sudden and unexpected shift of tracer uptake in the heart. However, none of these hypotheses could be verified with the available sheep datasets.

A question still left open is the transferability of these results to human studies. Further experiments would be needed to clarify whether the use of motion correction is as irrelevant as in this sheep study for relative LV wall quantification. A comparison of the non-corrected vs the motion-corrected reconstructions of animal and human datasets would be valuable to clarify this point. However, at present, all available human datasets showed a very irregular breathing pattern (acquired via a respiratory tracking system), with baseline drifts and sudden amplitude changes which made it impossible to perform accurate motion correction, without having to exclude a significant amount of the data. In addition to baseline drifts and unavoidable signal losses due to the nature of the breathing patterns of the patients, these external tracking devices also record the external motion of the abdomen, which needs to be translated into a corresponding internal motion of the heart. Improved motion correction techniques should be implemented in the first place, to allow an event-by-event motion correction such that the motion-corrected versus the static reconstructions could be analysed (e.g. as in [29]). **This, combined with cardiac motion compensation, and achieved**

441 within times that are compatible with clinical practice, could produce images
 442 with excellent noise properties. However, the heart motion is very non-rigid,
 443 and exact compensation for this motion is difficult. Proposed promising so-
 444 lutions to address this include the use of a cardiac deformation field from
 445 MR to reconstruct a single image from all gates [30, 31]. In the absence of
 446 accurate motion estimation, the risk of producing an inaccurate representa-
 447 tion of the heart is not negligible. In these cases, a great improvement could
 448 be already achieved if only respiratory motion compensation and a frame-by-
 449 frame reconstruction for the cardiac motion was performed, especially when
 450 in combination with non-anatomical priors. Seeing the beating heart could
 451 still be useful and have clinical value during the diagnosis, and we would
 452 expect that the end-systolic image (using all respiratory gates) would still be
 453 much better than a single double gated frame improperly corrected for. The
 454 additional combination of motion compensation with resolution modelling
 455 and non-anatomical priors would further improve cardiac wall homogeneities
 456 and quantitative accuracy.

457 **5. Conclusion**

458 We have explored the feasibility of an ex-to-in vivo comparison for the
 459 purpose of evaluating the benefits of combined motion and partial volume
 460 correction. The available data suggest that the use motion- and partial vol-
 461 ume correction techniques (e.g. MAP reconstruction with a well-tuned edge
 462 preserving prior, such as TV) does not hamper relative quantification and
 463 enhances the noise properties of the resulting images of the heart. It is ad-
 464 visable to use the end-systolic gate when quantification of cardiac datasets
 465 is aimed at, such that absolute quantification is improved.

466 **6. New knowledge gained**

467 This work addresses the previously unanswered question regarding the
 468 usefulness of non-anatomical priors in combination with motion correction for
 469 the quantification of cardiac PET images. *The study design that compares*
 470 *in vivo* cardiac datasets acquired on a clinical scanner to datasets on a pre-
 471 clinical small animal and therefore high resolution scanner is innovative and
 472 original.

473 7. Competing interests

474 The authors declare that they have no competing interests.

475 8. Author’s contributions

476 AT was responsible for the study design, the simulation setup, the recon-
477 structions and the data collection and analysis, and drafted the manuscript.
478 JD was also responsible for the data collection. JN and KV assisted with the
479 study design, the analysis of data and the careful revision of the manuscript.
480 JUV, FR, PC, JD and OG participated in the study design and critically
481 revised the manuscript. All authors read and approved the final manuscript.

482 9. Acknowledgements

483 The authors wish to thank Charles Watson, Judd Jones et al. for their
484 help with the Siemens data processing.

- 485 [1] T. H. Schindler, Cardiac PET/computed tomography applications and
486 cardiovascular outcome, PET clinics 10 (3) (2015) 441–459.
- 487 [2] K. Russell, M. Eriksen, L. Aaberge, N. Wilhelmsen, H. Skulstad, E. W.
488 Remme, K. H. Haugaa, A. Opdahl, J. G. Fjeld, O. Gjesdal, et al.,
489 A novel clinical method for quantification of regional left ventricular
490 pressure–strain loop area: a non-invasive index of myocardial work, Eu-
491 ropean heart journal 33 (6) (2012) 724–733.
- 492 [3] B. Nowak, A. M. Sinha, W. M. Schaefer, K. C. Koch, H. J. Kaiser,
493 P. Hanrath, U. Buell, C. Stellbrink, Cardiac resynchronization therapy
494 homogenizes myocardial glucose metabolism and perfusion in dilated
495 cardiomyopathy and left bundle branch block, J. Am. Coll. Cardiol.
496 41 (9) (2003) 1523–1528.
- 497 [4] A. Turco, J. Nuyts, J. Duchenne, O. Gheysens, J. Voigt, P. Claus,
498 K. Vunckx, Analysis of partial volume correction on quantification and
499 regional heterogeneity in cardiac PET, J. Nucl. Cardiol. 2017 .
- 500 [5] A. Chambolle, T. Pock, A First-Order Primal-Dual Algorithm for Con-
501 vex Problems with Applications to Imaging, J Math Imaging Vis 40 (1)
502 (2011) 120–145.

- [6] M. M. Ter-Pogossian, S. R. Bergmann, B. E. Sobel, Influence of cardiac and respiratory motion on tomographic reconstructions of the heart: implications for quantitative nuclear cardiology., *Journal of computer assisted tomography* 6 (6) (1982) 1148–1155.
- [7] M. A. Ahmed, P. Xiao, Q. Xie, New approach for simultaneous respiratory and cardiac motion correction in cardiac PET (NAMC-CPET), *Physics in medicine and biology* 60 (19) (2015) 7779.
- [8] F. Buther, M. Dawood, L. Stegger, F. Wubbeling, M. Schafers, O. Schober, K. P. Schafers, List mode-driven cardiac and respiratory gating in PET, *J. Nucl. Med.* 50 (5) (2009) 674–681.
- [9] T. Kokki, H. T. Sipilä, M. Teräs, T. Noponen, N. Durand-Schaefer, R. Klén, J. Knuuti, Dual gated PET/CT imaging of small targets of the heart: method description and testing with a dynamic heart phantom, *Journal of nuclear cardiology* 17 (1) (2010) 71–84.
- [10] J. Duchenne, P. Claus, A. Turco, K. Vunckx, E. Pagourelas, P. Haemers, J. Van Puyvelde, O. Gheysens, F. Rega, J. Voigt, A new animal model of rapid pacing-induced dilated cardiomyopathy and LBBB, *European Heart Journal - Cardiovascular Imaging* 16 (suppl 2) (2015) Abstract No. P145., ISSN 2047-2404.
- [11] J. Kim, HyperinsulinemicEuglycemic Clamp to Assess Insulin Sensitivity In Vivo, in: C. Stocker (Ed.), *Type 2 Diabetes*, vol. 560 of *Methods in Molecular Biology*, Humana Press, ISBN 978-1-934115-15-2, 221–238, 2009.
- [12] M. Dawood, F. Büther, N. Lang, O. Schober, K. P. Schäfers, Respiratory gating in positron emission tomography: a quantitative comparison of different gating schemes, *Medical Physics* 34 (7) (2007) 3067–3076.
- [13] A. M. Alessio, A. Rahmim, C. G. Orton, Resolution modeling enhances PET imaging, *Medical physics* 40 (12).
- [14] K. Vunckx, A. Atre, K. Baete, A. Reilhac, C. M. Deroose, K. Van Laere, J. Nuyts, Evaluation of three MRI-based anatomical priors for quantitative PET brain imaging, *IEEE transactions on medical imaging* 31 (3) (2012) 599–612.

- 535 [15] A. Turco, J. Nuyts, O. Gheysens, J. Duchenne, J.-U. Voigt, P. Claus,
536 K. Vunckx, Lesion quantification and detection in myocardial 18F-FDG
537 PET using edge-preserving priors and anatomical information from CT
538 and MRI: a simulation study, *EJNMMI physics* 3 (1) (2016) 1–32.
- 539 [16] B. De Man, S. Basu, Distance-driven projection and backprojection in
540 three dimensions, *Physics in medicine and biology* 49 (11) (2004) 2463.
- 541 [17] M. Brambilla, C. Secco, M. Dominietto, R. Matheoud, G. Sacchetti,
542 E. Inglese, Performance characteristics obtained for a new 3-dimensional
543 lutetium oxyorthosilicatebased whole-body PET/CT scanner with the
544 National Electrical Manufacturers Association NU 2-2001 Standard.,
545 *Journal of Nuclear Medicine*. 46 (12) (2005) 2083–91.
- 546 [18] G. Cheng, A. Alavi, E. Lim, T. J. Werner, C. V. Del Bello, S. R. Ak-
547 ers, Dynamic changes of FDG uptake and clearance in normal tissues,
548 *Molecular Imaging and Biology* 15 (3) (2013) 345–352.
- 549 [19] M. D. Cerqueira, N. J. Weissman, V. Dilsizian, A. K. Jacobs, S. Kaul,
550 W. K. Laskey, D. J. Pennell, J. A. Rumberger, T. Ryan, M. S. Verani,
551 et al., Standardized myocardial segmentation and nomenclature for to-
552 mographic imaging of the heart a statement for healthcare professionals
553 from the cardiac imaging committee of the Council on Clinical Cardi-
554 ology of the American Heart Association, *Circulation* 105 (4) (2002)
555 539–542.
- 556 [20] J. Nuyts, L. Mortelmans, P. Suetens, A. Oosterlinck, M. de Roo, Model-
557 based quantification of myocardial perfusion images from SPECT., *J*
558 *Nucl Med* 30 (12) (1989) 1992.
- 559 [21] D. G. Altman, J. M. Bland, Measurement in medicine: the analysis of
560 method comparison studies, *The statistician* (1983) 307–317.
- 561 [22] M. Rubeaux, M. K. Doris, A. Alessio, P. J. Slomka, Enhancing Car-
562 diac PET by Motion Correction Techniques, *Current cardiology reports*
563 19 (2) (2017) 14.
- 564 [23] D. Giavarina, Understanding Bland Altman analysis, *Biochemia medica*
565 25 (2) (2015) 141–151.

- [24] M. Taylor, T. R. Wallhaus, T. R. DeGrado, D. C. Russell, P. Stanko, R. J. Nickles, C. K. Stone, An evaluation of myocardial fatty acid and glucose uptake using PET with [18F] fluoro-6-thia-heptadecanoic acid and [18F] FDG in patients with congestive heart failure, *Journal of Nuclear Medicine* 42 (1) (2001) 55–62.
- [25] F. Lamare, A. Le Maitre, M. Dawood, K. Schäfers, P. Fernandez, O. Rimoldi, D. Visvikis, Evaluation of respiratory and cardiac motion correction schemes in dual gated PET/CT cardiac imaging, *Medical physics* 41 (7).
- [26] A. Martinez-Möller, D. Zikic, R. M. Botnar, R. A. Bundschuh, W. Howe, S. I. Ziegler, N. Navab, M. Schwaiger, S. G. Nekolla, Dual cardiac–respiratory gated PET: implementation and results from a feasibility study, *European journal of nuclear medicine and molecular imaging* 34 (9) (2007) 1447–1454.
- [27] F. Büther, M. Dawood, L. Stegger, F. Wübbeling, M. Schäfers, O. Schober, K. P. Schäfers, List mode–driven cardiac and respiratory gating in pet, *Journal of Nuclear Medicine* .
- [28] F. Gigengack, L. Ruthotto, M. Burger, C. H. Wolters, X. Jiang, K. P. Schafers, Motion correction in dual gated cardiac PET using mass-preserving image registration, *IEEE transactions on medical imaging* 31 (3) (2012) 698–712.
- [29] J. Cal-Gonzalez, M. Lassen, S. Rasul, D. Beitzke, K. Schaefer, M. Hacker, T. Beyer, Joint respiratory and cardiac motion compensation: application to cardiac PET/CT and PET/MR imaging., Paper presented at the International Conference on Nuclear Cardiology and Cardiac CT (ICNC, Vienna), 2017.
- [30] A. Rahmim, J. Tang, H. Zaidi, Four-dimensional image reconstruction strategies in cardiac-gated and respiratory-gated PET imaging, *PET clinics* 8 (1) (2013) 51–67.
- [31] T. Küstner, M. Schwartz, P. Martirosian, S. Gatidis, F. Seith, C. Gilliam, T. Blu, H. Fayad, D. Visvikis, F. Schick, et al., MR-based respiratory and cardiac motion correction for PET imaging, *Medical image analysis* 42 (2017) 129–144.