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Gating approaches in cardiac PET imaging

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Introduction.

Positron emission tomography (PET) is a powerful, quantitative imaging modality that has been used for decades to noninvasively investigate cardiovascular biology and physiology [1] The PET images are, however, affected by physiological patient motion which degrades the images qualitatively as well as quantitatively. Three distinct motion patterns can be observed in thoracic PET scans: cardiac contraction, respiratory motion, and patient repositioning during the acquisition. In this review, we discuss recent advances in cardiac and respiratory gating and provide an overview of the most promising recent developments in the field.

Clinical Background

Due to its superior sensitivity, spatial and temporal resolution compared to SPECT, PET has been considered a gold standard for non-invasive assessment of myocardial perfusion and viability [2,3] Its potential extends beyond the assessment of coronary artery disease (CAD) patients. PET facilitates early diagnosis of a broad range of cardiac conditions which affect the myocardium such as cardiomyopathies[4,5], infiltrative myocardial disease including sarcoidosis[6,7], and amyloidosis [8]. Furthermore, PET plays a key role in the detection of endocarditis[9] and inflammation related to implantable device infection [10]. Recently cardiac PET-imaging is also undergoing clinical validation in the assessment of unstable coronary plaques, which are at high risk of rupture [11-14].

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Modern PET systems

Aside from the development of novel tracers, the improvement in the clinical assessment of cardiac disease has partly been facilitated through the continuous improvement in the spatial resolution of the PET systems, which in current PET/CT systems offer resolutions of 2-5 mm at full-width at half maximum (FWHM) [15,16]. Correction for point spread function as well as time-of-flight imaging has become standard in many modern PET systems, which offer improved localization of the annihilation event and, thus, improved spatial recovery of the tracer distribution[17-20]. The high-resolution PET systems, in theory, permit accurate delineation of abnormal areas with a precision similar to the PET scanner's spatial resolution [11,12,21-23]. Unfortunately, high-resolution imaging of the myocardium is hampered by motion during the acquisitions [24]. The detrimental impact of motion during the PET-acquisition was recognized already in 1982 when it was proposed to divide the PET-data into motion-limited bins based on the respiratory/cardiac phase [25].

Since then several studies have investigated the effects of cardiac and respiratory motion [26-30]. The most investigated has been the correction for the cardiac contraction, despite the fact that other motion patterns have equally detrimental effects on image quality [31,32]. One reason for this is the potential need for additional equipment to track these motion patterns.

Cardiac gating:

Nowadays in the clinical setting usually 3-lead ECG is utilized [33]. With the lead data being directly transferred to the scanner both retrospective and prospective gating of the acquired PET is feasible. The use of 3-lead electrocardiograms (ECG) is relatively easy, cheap and has been shown to be reproducible in many studies [34]. Aside from the gating functionality it also serves to monitor the patient during the acquisition. The acquired ECG signal employs the R-wave as a reference to estimate the cardiac phase in which each coincidence was acquired, ultimately allowing the data to be sorted into near motion-free cardiac gates (Figure 1). Cardiac gating in most modern systems is performed retrospectively. Prospective gating is mainly used in older PET systems where listmode storage is not feasible and relies on defining phases in relation to the peak of the R wave. Such phases can be defined as preceding the R wave (backward gating) of occurring after it (forward gating). In both scenarios, the annihilation events can be sorted into predefined sinogram buffers and reconstructed once the acquisition is completed.

Cardiac gating can serve two functions: (1) it can be used for motion compensation of the myocardium [35] and (2) for functional assessment of the myocardium. The functional assessment provides both diagnostic and prognostic value in the clinical assessment of global cardiac function (left ventricular ejection fraction, LVEF), regional wall motion abnormalities and myocardial dyssynchrony [36,37]. The motion-compensated images are mainly used for research purposes while the functional assessments are used in the clinical routine. Analyses of the functional parameters have shown that an increase in LVEF (from baseline to peak stress) is inversely related to the magnitude of ischemia and the extent of angiographic CAD [38,39]. In patients with multivessel CAD, LVEF often shows a blunted response or can even drop on stress imaging. The change in LVEF during peak stress has been shown to have value for risk prediction [40,41]. In addition, cardiac gating has been proven a strong tool as a first approach in the assessment in the coronary plaques as the coronary arteries can shift up to 26 mm during the cardiac cycle [32,42,43] (Figure 2).

Respiratory Gating

Respiratory gating is desired in the clinical settings to improve image quality but is not often utilized in many modern systems which only allow for one form of gating during the reconstruction (ECG or respiratory gating). In systems facilitating dual-physiological trigger events (cardiorespiratory signals), the respiratory signal may be extracted using external markers such as piezo-electric respiratory belts or infra-red systems[24]. Other solutions employing spirometers, and measurements of the nasal temperature/humidity have also been successfully tested[44]. Respiratory gating employing external markers has several drawbacks. These include: a time-consuming imaging setup [45], potential malfunction during the acquisition [46] and rather rigid monitoring of the respiratory signal which results in less robust monitoring in patients with changes in the respiratory baseline [47]. Owing to the complex setups, the introduction of respiratory gating is still mainly a tool applied in research-studies primarily in centers with technical personnel who can maintain the systems.

To overcome the drawbacks of the external markers, the tendency in recent research is to replace the external markers using data-driven methods [34]. The data-driven methods offer several benefits over the use of external markers: First, the data-driven methods do not require frequent calibrations as they extract the respiratory signal directly from the list files [45]. Second, they allow for ad-hoc correction of all acquisitions acquired in listmode format, whereas careful planning is needed when using external markers. A third benefit is that the data-driven methods do not require the user to buy any additional hardware, which can be costly both to acquire and install.

In addition, the data-driven methods, in general, have the potential of facilitating accurate gating in patients with changes in the respiratory baseline, a frequent problem in myocardial perfusion imaging where stress scans are performed after administration of pharmaceutical agents. The common agents (Adenosine, Dipyridamole, and Regadenoson) all have short half-lives, which require optimized stressing protocols such that the maximum effect is obtained during the infusion of the PET-tracer. Given the fast roll-off effect of the pharmaceuticals, it is not uncommon to encounter changes in the respiratory baseline during the acquisition [48,49]. If not corrected for, the change in the respiratory baseline might introduce a degradation of the gated images in comparison to the non-gated images [50]. Here, data-driven gating approaches allow for tailored gating-approaches that fits the stress-imaging protocol and, thus, have the potential of outperforming the use of the external markers which often are calibrated to the respiratory baseline at the beginning of the acquisition [47,51].

Sensitivity based methods—The first attempts at extracting information of the respiratory motion directly from the PET-raw data (list files) were proposed by Bundschuh et al and He et al [52,53]. These methods, in brief, are based on the heterogeneous sensitivity profiles that exist in all PET-systems. The sensitivity profile is partly introduced by the geometry of the system and partly by the detector materials used [54]. Owing to the geometry in the PET system, the highest sensitivity is obtained in the center of the field of view. Heterogeneous objects moving in and out of the center field of view will result in changes in the obtained count rates equivalent to the motion in the scanners axial direction. For patient scans, the heterogeneous uptake rates are obtained through differences in the tracer distribution as well as differences in the linear attenuation coefficients in the lungs and diaphragm.

Center-of-Mass/centroid-of-mass based methods—The center-of-mass or centroid-of-mass (CoM) based approaches have gained substantial interest in imaging of organs with focal uptake and high contrast to background ratio, such as myocardial scans and in studies of non-small cell lung cancers. Several methods relying on this assessment have been proposed, using either the full field of view or through detection of localized motion vector fields [44,55]. The CoM assessment, in brief, evaluates the centroid of the counts obtained in the region of interest using singleslice rebinned sinograms (SSRB)[56], which are marked by the user in most cases. The SSRB algorithm, in short, is an algorithm that compresses the full 3D sinograms into a reduced 3D sinogram. By performing the compression, the noise is reduced and provides a more stable respiratory signal. This omits the varying sensitivity profiles and, thus, provides a more stable measurement of the respiratory cycle even for lesions slightly misplaced from the center of the systems field of view.

Sinogram Fluctuation model—The sinogram fluctuation model evaluates the fluctuations obtained in sinograms with short time duration (~500ms). Following their binning, the sinograms can be evaluated for the periodicity of the signal changes in each of the short time-duration datasets, thus, permitting extraction of the respiratory signal using only data with frequencies within the normal respiratory range (2-9 s periodicity) [57].

MR-based approaches—The introduction of the hybrid PET/MR systems has facilitated new methods for motion detection approach, in which accurate estimates of the respiratory signal can be extracted directly from the diaphragm in the PET-images [58-61]. The respiratory signal can be obtained from either dedicated MR sequences that target the golden angle [58], or through tracking of the heart/diaphragm in standard MR-sequences [62]. The resulting data can be used either for respiratory gating or for motion compensation during the image reconstruction [29,58]. Despite the accurate tracking of both respiratory and cardiac motion through dedicated MR sequences, the MR-based approaches have some drawbacks. They can only be utilized in integrated PET/MR systems, and often require specific MR-sequences for motion detection, which can limit the time left for the acquisition of clinically important data [58].

Respiratory gating: Phase vs amplitude.: Once acquired, the respiratory signal can be used for gating in multiple ways where phase-based/time-based (similar to the ECG-based gating approaches) and amplitude-based gating are the two most common approaches (Figure 3) [51].

Time-based / Phase-based gating: The phase-based method is the most simplistic method of the two, where each respiratory phase is divided into a user-defined number of phases, each with equal time-duration [51]. This ensures homogeneous noise-levels for all gates, which is beneficial in the subsequent analyses. Unfortunately, this method does not allow for differentiating between normal tidal breathing and sudden excessive in/expiratory breath-holds or changes in the respiratory baseline.

Amplitude-based gating: The amplitude-based gating offers more accurate gating than the time-based/phase-based gating approach. Despite the superiority in providing high spatial differentiation of data from different respiratory amplitudes, this technique also has its limitations. The highly dynamic range of respiratory signals often hampers its functionality and, thus, most often requires truncation or discarding of data outside the normal range to ensure enough counts to provide clinical image-qualities. In addition, the asynchronous respiratory cycle will often introduce inhomogeneities in the noise-characteristics in the resulting gated images with the best quality often obtained in the end-expiratory phase. Due to this, it has been proposed to use the optimal respiratory gate, which only employs data from the end-expiratory phase – known as the optimal respiratory phase, which typically can contain up to 35% of all image counts [63].

Dual gating

The single gating techniques have been proven suboptimal for many PET-scans as the non-corrected motion-pattern is still embedded in the resulting images. Dual-gating approaches, which combine the cardiorespiratory motion, have been proposed [26,64-66]. The combination of the two gating techniques ensures virtually motion-free images, with only little intra-gate motion present (Figure 4). Unfortunately, this requires sufficient image quality (count rates per single gate) in the subsequent reconstructions, as often up to 16-64 gates are being utilized. The exact number depends on how many respiratory and cardiac gates are used ($N_{Respiratory}$ gates × $N_{cardiac}$ gates) [67,68], with N being the number of the respective gates.

PET attenuation correction issues resulting from motion

Attenuation correction (AC) is an important prerequisite for absolute quantification in all PET imaging. Several attenuation correction techniques have been proposed, depending on the modality (PET-only, PET/CT or PET/MRI) [69-71]. Several drawbacks and limitations have been described for the AC maps, disregarding the acquiring modality. The drawbacks include both physiological and technical aspects such as beam-hardening, misalignment, truncation as well as non-physiological artifacts. In the context of gating, especially the misalignment artifacts are particularly relevant. The remaining artifacts have a more general character and have been discussed thoroughly elsewhere [72,73].

Misalignment of the PET-emission data and the AC-images can be classified either as repositioning events where the patient moves between the acquisition of the AC maps and the PET-emission data, differences between the respiratory-gated PET-images and the corresponding AC maps or as breathing during the AC acquisition (Figure 5) [74-76].

Respiratory motion during the PET-images translates the heart up by up to a few centimeters (see section Respiratory gating). Due to the fast acquisition times of the AC images (a few seconds in CT, 30s in PET/MR systems), respiratory motion during the acquisition is often not a problem regardless whether a free-breathing or end-expiratory breath-hold acquisition protocol is utilized [77]. Several optimizations of AC acquisitions have been proposed for both the PET/MR and PET/CT systems. Employing cine CT for PET/CT has been suggested [78]. This allows reconstructing a respiratory-averaged AC map with the same displacements as obtained during the cine CT acquisition. In PET/MR systems, it has been proposed to acquire several AC maps in different respiratory positions as the AC images are acquired without the use of ionizing radiation.

New gating techniques and challenges ahead

Cardiorespiratory motion has been investigated by many researchers and several gating approaches have been proposed. The use of external markers has been used in the conventional assessment of the displacement during the acquisition. However, recent trends indicate that data-driven gating techniques are an emerging technology that will permit marker-less motion detection in clinical routine. These gating techniques mainly focus on respiratory motion detection, though cardiac gating might also be possible as demonstrated for the first time in 2009 [34,44]. While these established techniques might replace the conventional external marker methods, the potential of data-driven detection of patient repositioning events is another interesting field of research. A recent pilot study has shown that such techniques are feasible in coronary plaque studies, in which gross patient motion has a detrimental effect on the quantitative accuracy [79]. Furthermore, it is believed that also tracer-kinetic studies for novel PET-tracers which scanning protocols can last up to one hour or more will benefit from patient repositioning detection, ultimately enabling triple-gating or application of sophisticated combinations of various gating techniques [80].

Moreover, the use of gated images is expected to be implemented in motion compensation techniques, either during or before image-reconstruction. This will improve the image quality of the static images, where accurate definition of pathophysiological changes can be difficult in the gated images due to the increased noise levels. By correcting for the motion during image-reconstruction, it is possible to obtain a fully motion compensated image with the spatial resolution similar to gated images, with the noise characteristics of the static image-acquisitions. In addition, the motion compensated images can also reduce the respiratory blur in the ECG-gated reconstructions and, thus, lead to improved quantification of left ventricular volumes for function assessments. Therefore, gating will become increasingly important in the future not only for the definition motion but also in the pursuit of accurate assessment of physiological parameters.

Summary:

In this article gating approaches for both cardiac and respiratory motion have been reviewed. Cardiac gating has enabled accurate heart and coronary imaging now respiratory gating has become an important frontier in PET imaging. With multiple limitations of currently utilized external marker methods and the increasing availability of list mode PET data, the field is now moving towards data-driven methods which emerge as a promising alternative. Ultimately dual gating encompassing both cardiac and respiratory motion or even triple gating which also takes into account gross patient motion effects shall lead to further improvements in image quality.

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Key points

Cardiac and respiratory motion have a detrimental effect on cardiovascular PET imaging and affect both quantitative and qualitative PET measures.

Gating can ameliorate the unfavorable impact of motion additionally enabling evaluation of left ventricular systolic function (ejection fraction) and wall motion abnormalities.

Cardiac gating is used in the clinical setting while respiratory motion gating remains a research tool.

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Synopsis:

Cardiac Positron Emission Tomography (PET) provides high sensitivity and high negative predictive value in the diagnosis of coronary artery disease and cardiomyopathies. Cardiac, respiratory as well as bulk patient motion have detrimental effects on thoracic PET-imaging, hereunder cardiovascular PET imaging where the motion can affect the PET images quantitatively as well as qualitatively. Gating can ameliorate the unfavorable impact of motion additionally enabling evaluation of left ventricular systolic function. In this article, we review the recent advances gating approaches and highlight the advances in data-driven approaches which hold promise in motion detection without the need for complex hardware setup.

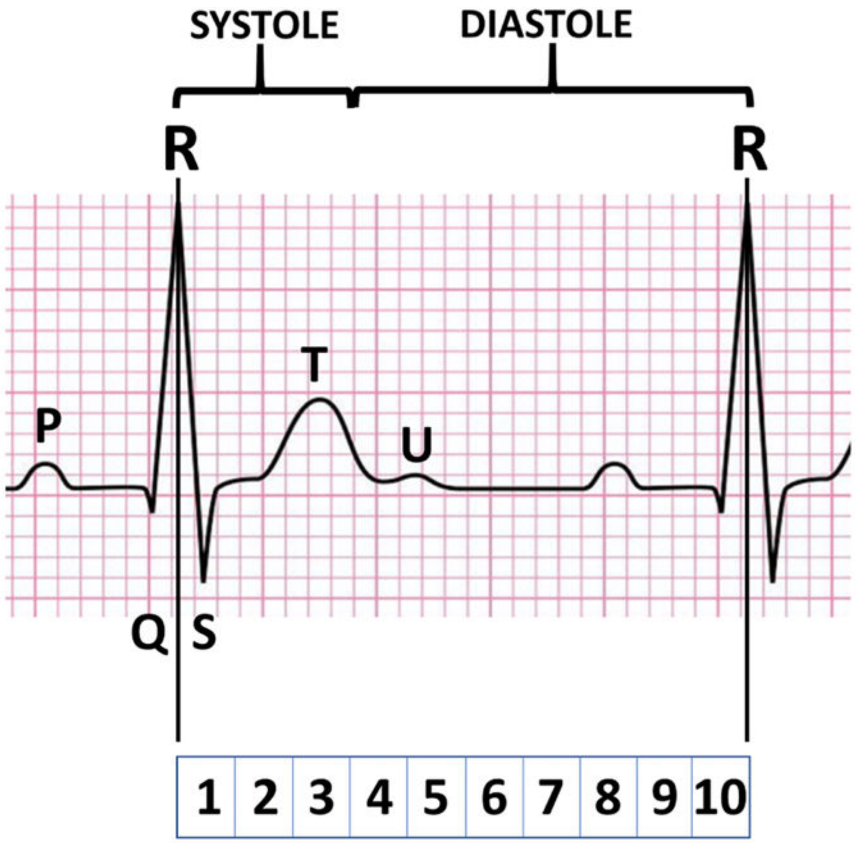

Figure 1.
Principle of ECG-gating, here shown using an 8-bin ECG-gating. The acquired PET-data for each R-R interval is divided into a user-specified number of phases of the cardiac contraction.

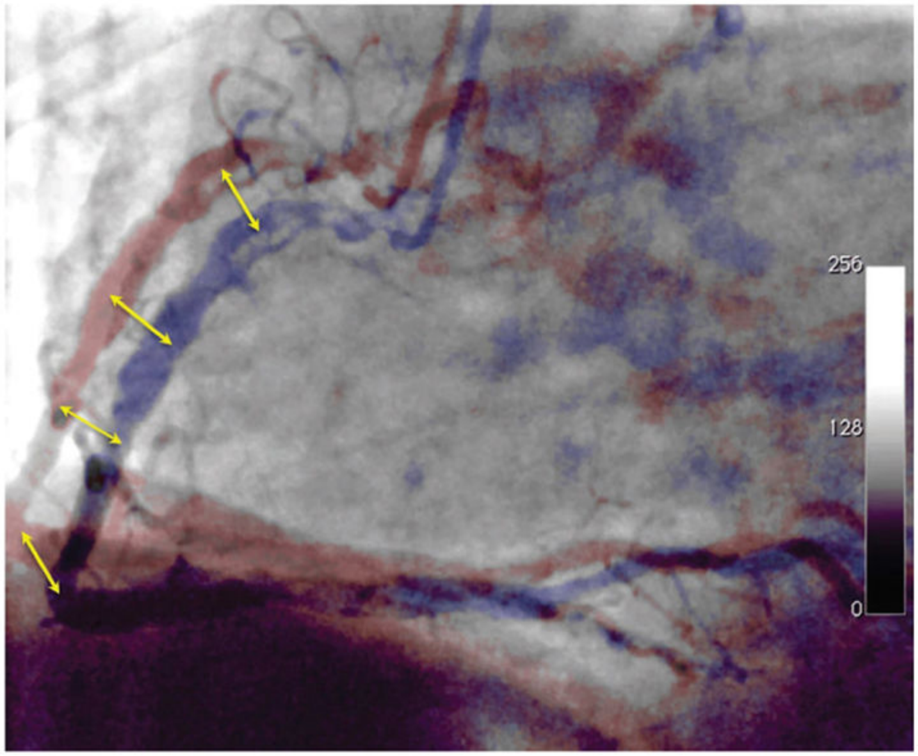

Figure 2.
Displacement of the coronary arteries during the cardiac contraction. The coronary arteries are shifting 8-26 mm during cardiac contraction (yellow arrows).

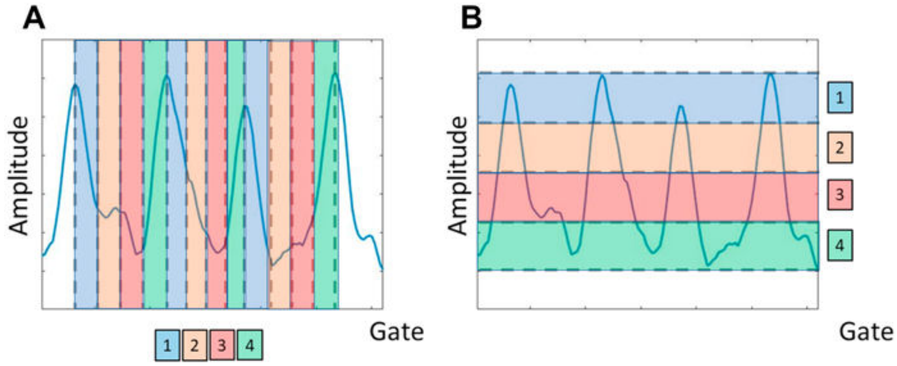

Figure 3.

Time-based (phase-based) gating and amplitude-based gating techniques, here exemplified using 4 respiratory gates. (A) time-based method divides the data into equally time-divided bins that will have the same noise properties (equal time-duration). (B) amplitude based gating divides the data into bins with the same respiratory amplitude, and thereby pose the risk of having noise-variated gates in the following assessments, as can be observed for the third respiratory cycle which does not reach the same amplitude as the preceding cycles.

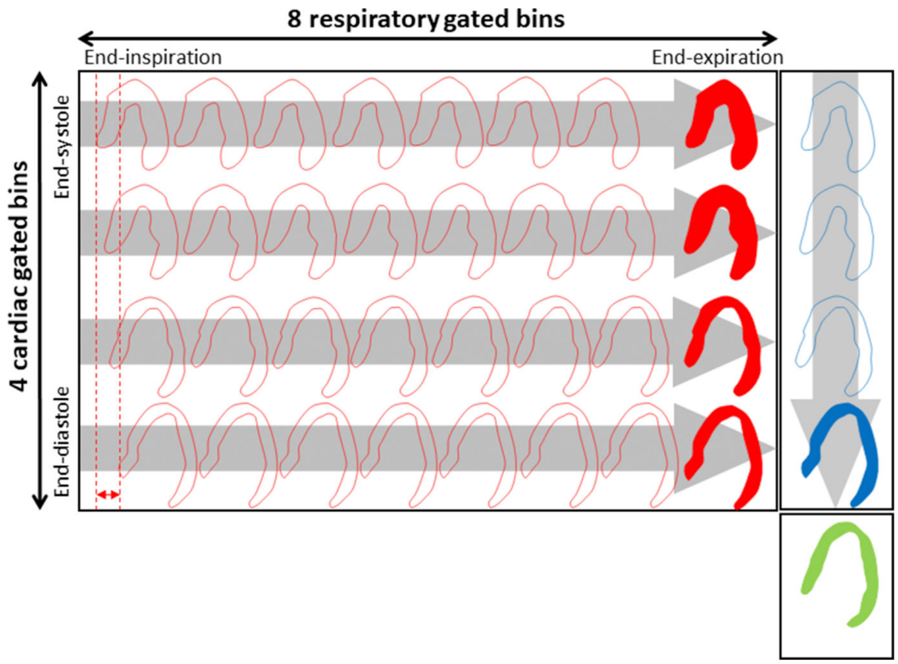

Figure 4.
Dual-gating scheme. Example of a dual gating scheme employing 4 ECG and 8 respiratory bins, which creates a total of 24 virtually motion-free images. Each of the gated images can be coregistered to obtain images with reduced noise properties when compared to the noise in each individual gate. This research was originally published in *JNM*. Slomka PJ, Rubeaux M, Le Meunier L, et al. Dual-Gated Motion-Frozen Cardiac PET with Flurpiridaz F18. J Nucl Med. 2015;56(12): 1876-1881. © SNMMI.

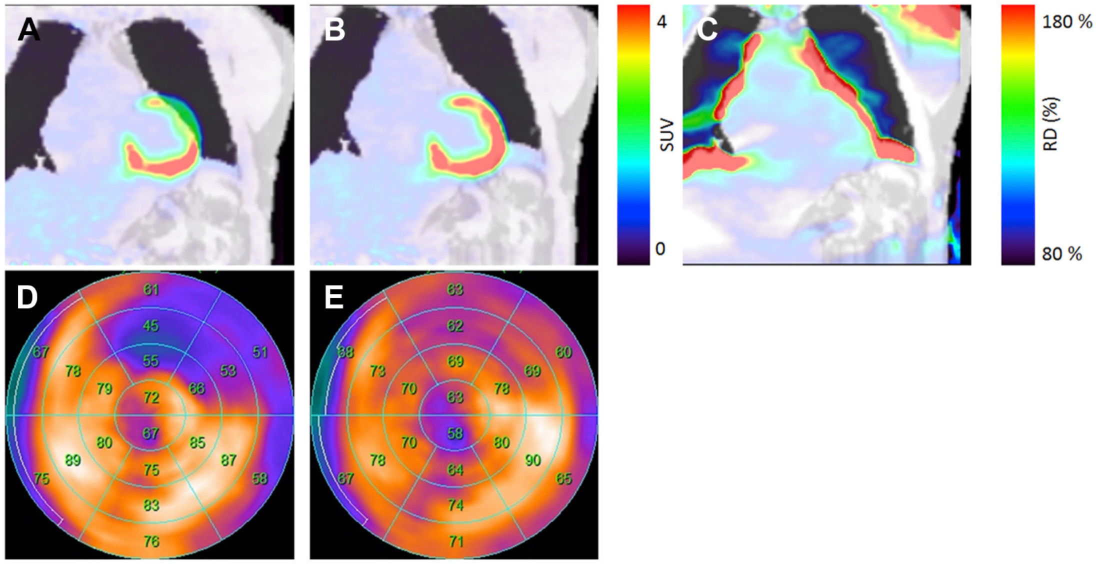

Figure 5.

Displacement of PET-emission data and the attenuation correction (AC) maps (A) can cause local changes of more than 80% in the quantitative assessment (B, C). Correction for the misalignment of the AC maps and PET-data reduced the extent and severity of the hypometabolic region (D, E). The displacements can be introduced through respiratory motion during the PET-acquisition or by patient repositioning between the acquisition of the AC map and the PET data. This figure was originally published in *JNC* under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/). Lassen ML, Rasul S, Beitzke D, et al.: Assessment of attenuation correction for myocardial PET imaging using combined PET/MRI. J Nucl Cardiol. 2017:1-12 © The Author(s) 2017.