Use of a single \([^{11}\text{C}]-\text{meta}-\text{hydroxy-ephedrine}\) scan protocol for assessing flow innervation mismatch in patients with ischemic cardiomyopathy

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Abstract

Mismatch between areas of reduced myocardial blood flow (MBF) and reduced myocardial innervation (‘defect’ areas) may be used to predict ventricular arrhythmias. The presence of a mismatch zone can be derived from a combined protocol consisting of both an MBF and $^{11}$C-meta-hydroxyephedrine ($^{11}$C-HED) scans. The rate of influx of $^{11}$C-HED from blood to myocardium ($K_1$) is proportional to MBF and could potentially be used as an index for defining perfusion defects. The aim of this study was to assess whether $K_1$ derived from an $^{11}$C-HED scan can be used as an index of MBF, allowing for a single $^{11}$C-HED scan protocol for defining MBF-innervation mismatch areas.

Methods: 17 patients with known ischemic cardiomyopathy underwent dynamic $^{15}$O-H$_2$O and $^{11}$C-HED scans. Discrete arterial blood samples were taken during $^{11}$C-HED scans for metabolite correction of the image derived input function. $^{11}$C-HED influx rate was obtained using a single tissue compartment model and compared to transmural MBF ($MBF_T$), defined as MBF multiplied by perfusable tissue fraction. Defect sizes were obtained from parametric $K_1$ and $MBF_T$ images, using 50% of a remote control segment as cut-off value.

Results: There was a significant correlation of $MBF_T$ and $K_1$ ($r^2 = 0.65$, slope = 0.40, $p < 0.001$) although $K_1$ was significantly lower than $MBF_T$ (slope of the linear fit significantly different from 1, $p < 0.001$). In addition, correlation between $MBF_T$ derived and $K_1$ derived defect sizes was high ($r^2 = 0.91$, slope = 0.90, $p < 0.001$) with no significant difference in defect size based on $K_1$ or $MBF_T$ (20.9±11.3% and 20.1±10.7% for $MBF_T$ and $K_1$, respectively, $p = 0.80$).

Conclusion: $^{11}$C-HED influx rate $K_1$ can be used as an alternative to a separate MBF scan for assessing mismatch areas between reduced MBF and reduced myocardial innervation. This eliminates the use of a separate MBF scan and consequently reduces scan duration, radiation dose and risk of patient motion between scans.
10.1 Introduction

There has been renewed interest in non-invasive imaging of myocardial sympathetic innervation for the prediction of life threatening ventricular arrhythmias or implantable cardioverter defibrillator (ICD) discharges using PET (182–186) or SPECT (187–189). It has been shown that, in myocardial infarction (MI), the area of reduced innervation often exceeds the area of reduced myocardial blood flow (MBF) (60, 62, 190, 191, 193, 194). Furthermore, in a porcine model of MI, it has been shown that occurrence of such MBF-innervation mismatch zones is related to inducible ventricular tachycardias originating from these zones (58). Therefore, non-invasive imaging of MBF-innervation mismatch zones may play a major role in risk stratification of patients with ischemic cardiomyopathy that are scheduled for ICD implantation.

In general, MBF-innervation mismatch zones are measured using separate MBF and innervation scans. The use of two separate scans, however, has some disadvantages: motion artefacts between scans may occur, overall study duration is prolonged and radiation dose to the patient is increased. Furthermore, differences in region of interest (ROI) definitions between scans may affect defect and mismatch sizes and consequently accuracy of risk profiles. Clearly, a single scan protocol for defining MBF-innervation mismatches would be preferable.

Recently, it has been shown that the kinetics of $^{11}$C-meta-hydroxyephedrine ($^{11}$C-HED) can be described reliably using a single tissue compartment model with corrections for left and right ventricular spill-over (Chapter 7 of this thesis). The underlying tracer kinetic model has two parameters: $K_1$ and $k_2$, which represent the rate of $^{11}$C-HED transfer from blood to myocardium (influx rate) and the rate of transfer from myocardium to the blood (clearance rate), respectively. The volume of distribution of $^{11}$C-HED, defined as the ratio of $K_1$ and $k_2$, represents net uptake, i.e. equilibrium distribution between tissue and plasma, and can be used as a measure of innervation. $K_1$ is dependent on both the extraction fraction of $^{11}$C-HED and MBF. Therefore, if the extraction fraction of $^{11}$C-HED is constant across a clinically relevant range of (resting) MBF levels, changes in $^{11}$C-HED $K_1$ would reflect changes in MBF. In this case a single $^{11}$C-HED scan protocol could be used to define MBF-innervation mismatch areas. Therefore, the aim of this study was to assess whether $K_1$ derived from an $^{11}$C-HED scan can be used as an index of MBF.

10.2 Materials and methods

10.2.1 Patient population

17 patients (mean age 67, range 43–80 years; 13 males) with ischemic cardiomyopathy and a left ventricular ejection fraction below 35% based on cardiac magnetic resonance imaging (MRI) were included. Ischemic cardiomyopathy was defined as having one or more stenoses > 50% as determined from a coronary angiogram and delayed contrast enhancement on cardiac MRI. The study was
approved by the Medical Ethics Review Committee of the VU University Medical Center, and all participants gave written informed consent prior to inclusion.

10.2.2 Scanning protocol

Patients underwent a dynamic $[^{15}\text{O}]\text{H}_2\text{O}$ scan, followed by a $[^{11}\text{C}]\text{HED}$ scan in the same session. All studies were performed on a Gemini TF–64 (Philips Healthcare, Best, The Netherlands) PET/CT scanner (66).

A 5 mL bolus injection of 370 MBq $[^{15}\text{O}]\text{H}_2\text{O}$ (0.8 mL s$^{-1}$), followed by 35 mL saline (2 mL s$^{-1}$), was administered simultaneously with the start of a list-mode emission scan of 6 minutes. The injected dose was chosen to remain within the linear range of the scanner, the upper limit of which is at a singles count rate of about 35 Mcps (153). Maximum singles count rates in the present study were approximately 32 Mcps during the first pass of the bolus. This PET scan was followed immediately by a respiration-averaged low dose (LD) CT scan (55 mAs, rotation time 1.5 s, pitch 0.825, collimation 64x0.625, acquiring 20 cm in 11 s compared to 4 s for a regular LD-CT) during normal breathing. The emission scan was reconstructed into 22 frames (1x10, 8x5, 4x10, 2x15, 3x20, 2x30 and 2x60 s) using the 3D row action maximum likelihood algorithm (3D RAMLA) and applying all appropriate corrections for scanner normalization, dead time, decay, randoms, scatter and attenuation, the latter based on the corresponding LD-CT scan. Frames consisted of 45 planes of 144x144 voxels with voxels having a dimension of 4x4x4 mm.

$[^{11}\text{C}]\text{HED}$ was synthesized as described previously (Chapter 7 of this thesis). 370 MBq $[^{11}\text{C}]\text{HED}$ was injected as a 5 mL bolus (0.8 mL s$^{-1}$) followed by a 35 mL saline flush (2 mL s$^{-1}$), simultaneously starting a 60 min list-mode emission scan. A slow low-dose CT scan was performed after each emission scan to correct for attenuation, similar as for the $[^{15}\text{O}]\text{H}_2\text{O}$ scan. Images were reconstructed into 36 frames (1x10, 8x5, 4x10, 3x20, 5x30, 5x60, 4x150, 4x300, 2x600 s) using 3D-RAMLA, applying all appropriate corrections.

10.2.3 Blood sampling

Prior to the scanning session, all patients received an indwelling radial artery cannula for withdrawal of discrete blood samples during the dynamic $[^{11}\text{C}]\text{HED}$ scan. A total of 7 arterial samples of 7 mL each were collected at 2.5, 5, 10, 15, 20, 30, 40 and 60 min $[^{11}\text{C}]\text{HED}$ post-injection. Blood samples were analysed for blood and plasma concentrations and for radiolabelled plasma metabolites of $[^{11}\text{C}]\text{HED}$ as previously described (219).

10.2.4 Input functions

Input functions were obtained using in-house developed software. For both $[^{15}\text{O}]\text{H}_2\text{O}$ and $[^{11}\text{C}]\text{HED}$, one cm diameter ROIs were placed over the ascending aorta in at least 5 transaxial image planes in the frame showing the first pass of the injected bolus. These ROIs were combined in one volume of interest
10.2. Materials and methods

(VOI) for the ascending aorta. A second set of ROIs was placed over the right ventricular (RV) cavity in 5 transaxial planes, with ROI boundaries at least 1 cm from the RV wall to avoid spill-over of myocardial activity. Again these ROIs were combined into one RV VOI. Both VOIs were then transferred to the full dynamic images to obtain arterial whole blood \( (C_A(t)) \) and RV \( (C_{RV}(t)) \) time-activity curves. Next, for \( ^{11}\text{C}\)HED only, plasma/whole blood ratios derived from the manual samples were fitted to a sigmoid function. Parent fractions derived from these manual samples were fitted to a sigmoid function. Finally, the parent plasma curve \( (C_P(t)) \) was obtained by multiplying \( C_A(t) \) with fitted plasma/whole blood ratio and parent fraction curves.

10.2.5 Segmental analysis

Sixteen myocardial segments, excluding the most distal apex segment, were drawn manually on short-axis images according to the 17-segment model of the American Heart Association (169), using software developed in-house within Matlab 7 (Mathworks, Natick, MA, USA). For \( ^{15}\text{O}\)H\(_2\)O, segments were defined on the final frame of the dynamic images whilst for \( ^{11}\text{C}\)HED, parametric images of perfusable tissue fraction (PTF) were used. Obtained segment templates were projected onto all frames of their corresponding short-axis dynamic emission scans to extract segmental TACs. TACs were fitted to a single tissue compartment model for both \( ^{15}\text{O}\)H\(_2\)O and \( ^{11}\text{C}\)HED using standard nonlinear least squares regression according to equations 10.1 and 10.2 for \( ^{15}\text{O}\)H\(_2\)O (107) and \( ^{11}\text{C}\)HED (Chapter 7 of this thesis), respectively:

\[
C_{PET}(t) = \text{PTF} \cdot \text{MBF} \cdot C_A(t) \otimes e^{-\frac{\text{MBF}}{\text{PTF}} \cdot t} + V_A \cdot C_A(t) + V_{RV} \cdot C_{RV}(t) \tag{10.1}
\]

\[
C_{PET}(t) = K_1 \cdot C_P(t) \otimes e^{-k_2 \cdot t} + V_A \cdot C_A(t) + V_{RV} \cdot C_{RV}(t) \tag{10.2}
\]

in which \( C_{PET}(t) \), \( C_A(t) \), \( C_{RV}(t) \) and \( C_P(t) \) represent radioactivity concentrations in tissue, whole blood, right ventricular blood and parent tracer in plasma, respectively. PTF represents perfusable tissue fraction, \( V_A \) left ventricular spillover and \( V_{RV} \) right ventricular spillover. For \( ^{15}\text{O}\)H\(_2\)O, \( V_T \) was fixed to 0.91 mL\( g^{-1} \) (10) whilst for \( ^{11}\text{C}\)HED, \( V_T \) was calculated as \( K_1/k_2 \).

Since MBF represents perfusion in perfusable tissue (103) and \( K_1 \) represents \( ^{11}\text{C}\)HED influx in both perfusable and non-perfusable myocardial tissue, MBF was multiplied by PTF to obtain perfusion in all myocardial tissue (MBF\(_T\)). PTI was calculated according to (82):

10.2.6 Parametric images

For \( ^{15}\text{O}\)H\(_2\)O, parametric images were generated using a basis function implementation (81,131,132) of the single tissue compartment model (eq 10.1) with corrections for blood volume, spill-over (27) and for perfusable tissue fraction (28). 100 basis functions were used with exponentially spaced values of MBF/\( V_T \) between 0.1 and 2.5 min\(^{-1}\). For \( ^{11}\text{C}\)HED, a basis function implementation of
Figure 10.1. Correlation between $K_1$ of $[^{11}\text{C}]$HED and absolute MBF on the heart segment level. This correlation was significant ($r^2=0.65$, $p < 0.001$) and the slope of the linear fit was 0.40, which was significantly lower than 1 ($p < 0.001$).

\[ eq 10.2 \]

was used (Chapter 9 of this thesis), using 100 basis functions with exponentially spaced values of $k_2$ between 0.002 and 0.1 min$^{-1}$ and corrections for left and right ventricular spill-over. For $[^{11}\text{C}]$HED, parametric images of $V_T$ were obtained by dividing parametric images of $K_1$ by parametric images of $k_2$. For both $[^{11}\text{C}]$HED and $[^{15}\text{O}]\text{H}_2\text{O}$, parametric images of anatomical tissue fraction (ATF) were generated according to \( eq \ 10.3 \)

\[
ATF = 1.06 \cdot (CT_{\text{norm}} - V_A - V_{RV})
\]

In which $CT_{\text{norm}}$ represents the normalized LD-CT scan and 1.06 represents density of blood. In voxels with $V_A+V_{RV} > 0.75$, $V_A$ or $V_{RV} > 0.60$ or ATF $< 0.25$, MBF, $K_1$ and $V_T$ were set to zero in order to avoid spurious noise induced high values outside the heart or in blood vessels as described previously (81,82). Finally, MBF$_T$ images were obtained by multiplying MBF images with PTI images.

10.2.7 Data analysis

Correlation between MBF$_T$ and $K_1$ was assessed using linear regression. Based on visual analysis of segmental data, for each patient 2 to 4 remote, non-infarcted segments were defined manually and used as control region. For both MBF$_T$ and $K_1$, defect size was defined as the percentage of pixels below a percentage (between 20 and 80%, in increments of 5%) of the average of the control region. Similarly, parametric $V_T$ images were obtained and used to define innervation defects using the same control region. Innervation-perfusion mismatch sizes were obtained by subtracting the $K_1$ or MBF$_T$ defect size from $V_T$ defect size. To avoid differences in VOI definition between $[^{11}\text{C}]$HED and $[^{15}\text{O}]\text{water}$
10.3 Results

Table 10.1. Overview of correlations, slopes and intercepts of the linear fits, p-value based on paired Wilcoxon rank test, and Dice similarity coefficient (DSC) for defect sizes based on MBF_T and K_1 for different relative cut-off values. * denotes a slope significantly different from 1 (p < 0.05)

<table>
<thead>
<tr>
<th>Relative cut-off</th>
<th>r²</th>
<th>slope</th>
<th>intercept</th>
<th>slope, intercept=0</th>
<th>p</th>
<th>DSC</th>
</tr>
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<tr>
<td>20%</td>
<td>0.65</td>
<td>0.63*</td>
<td>0.77</td>
<td>0.72*</td>
<td>0.62</td>
<td>0.95</td>
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<tr>
<td>25%</td>
<td>0.77</td>
<td>0.74*</td>
<td>0.81</td>
<td>0.81*</td>
<td>0.77</td>
<td>0.94</td>
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<td>30%</td>
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<td>0.80</td>
<td>0.90</td>
<td>0.87</td>
<td>0.93</td>
</tr>
<tr>
<td>35%</td>
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<td>0.88</td>
<td>0.72</td>
<td>0.92*</td>
<td>0.89</td>
<td>0.92</td>
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<tr>
<td>40%</td>
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<td>0.73</td>
<td>0.95</td>
<td>0.65</td>
<td>0.91</td>
</tr>
<tr>
<td>45%</td>
<td>0.94</td>
<td>0.90</td>
<td>1.15</td>
<td>0.95</td>
<td>0.75</td>
<td>0.90</td>
</tr>
<tr>
<td>50%</td>
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<td>1.37</td>
<td>0.95</td>
<td>0.80</td>
<td>0.88</td>
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<td>55%</td>
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<td>1.78</td>
<td>0.95</td>
<td>0.80</td>
<td>0.86</td>
</tr>
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<td>60%</td>
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<td>2.70</td>
<td>0.95</td>
<td>0.84</td>
<td>0.85</td>
</tr>
<tr>
<td>65%</td>
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<td>3.79</td>
<td>0.95</td>
<td>0.84</td>
<td>0.83</td>
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<tr>
<td>70%</td>
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<td>5.19</td>
<td>0.98</td>
<td>0.87</td>
<td>0.82</td>
</tr>
<tr>
<td>75%</td>
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<td>0.84</td>
<td>6.92</td>
<td>0.99</td>
<td>0.97</td>
<td>0.80</td>
</tr>
<tr>
<td>80%</td>
<td>0.74</td>
<td>0.83</td>
<td>8.71</td>
<td>1.00</td>
<td>0.97</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Scans, defect sizes were assessed for the entire LV rather than for each segment individually. Correlation and agreement between defect sizes were assessed using linear regression, Bland Altman analysis and paired Wilcoxon rank tests. Finally, Dice similarity coefficients (DSC) were calculated for the polar maps to quantify agreement in both defect location and size.

10.3 Results

Scans of two patients showed visually identifiable motion and were excluded from further analysis. For the remaining 15 patients, correlation between absolute MBF_T and K_1 is presented in Figure 10.1. As can be seen, there was a significant correlation between MBF_T and K_1 (r²=0.65, p<0.001). The slope of the linear fit was 0.40 and significantly lower than 1 (p<0.001), indicating that the extraction fraction of [11C]HED is relatively constant across the range of MBF_T values encountered.

Typical examples of parametric MBF_T and K_1 images are shown in Figure 10.2, indicating reduced MBF_T and K_1 in the territory of the left anterior descending artery. Corresponding polar plots are shown in Figure 10.3, with defect areas indicated as black in Figures 10.3C and 10.3D. Correlation between defect sizes was high (r²=0.91, p < 0.001, Figure 10.4A) and Blant Altman analyses showed a 95% confidence interval including 0 (Figure 10.4B), using a 50% cut-off. The slope of the linear fit was 0.90 and not significantly different from 1 (p = 0.24). In addition, the intercept of the regression line was 1.37 and not significantly different from 0 (p = 0.50). A paired Wilcoxon rank test showed that defect sizes based on K_1 were not significantly different from those based on MBF_T (p = 0.80). In addition, when the linear fit was forced through...
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Figure 10.2. Typical example of parametric images of MBF$_T$ (top) and $K_1$ (bottom) of a patient with a myocardial infarct in anterior, septal and apical walls.

the origin, the slope was 0.95, which was still not significantly higher than 1 ($p = 0.20$) indicating no significant differences in defect sizes. DSC (0.88±0.05, range 0.77-0.96) showed good agreement between MBF$_T$ and $K_1$ at the polar map level, indicating that defect locations were similar. For the all relative cut-off values, correlations, slopes and intercepts of the linear fit, p-values of paired Wilcoxon rank tests and average DSC are shown in table 10.1. Figure 10.5 shows correlation between mismatch zones derived using MBF$_T$ and $K_1$. A high correlation between mismatch zones was found ($r^2 = 0.85$, $p < 0.001$) with slope and intercept were not significantly different from 1 ($p=0.32$) and 0 ($p=0.21$), respectively. In addition, paired Wilcoxon rank test showed that mismatch zones were not significantly smaller for $K_1$ than for MBF$_T$ ($p=0.80$).

10.4 Discussion

In the present study, a method to assess myocardial blood flow-innervation mismatch zones from a single $^{11}$C HED scan was studied, using the influx rate $K_1$ of $^{11}$C HED to obtain an index of MBF rather than measuring MBF separately using an additional $^{15}$O H$_2$O scan. The proposed method eliminates the risk of motion between scans and differences in ROI definition, reduces radiation burden to the patient and increases patient throughput while providing accurate data on mismatch areas.

Direct comparison between $K_1$ and MBF$_T$ (transmural MBF i.e. MBF in
10.4. Discussion

Figure 10.3. Polar maps of $MBF_T$ (left) and $K_1$ (right) of the same patient as in figure 2. At the bottom row, the defect area is indicated. The total defect size was 28.7% based on $MBF_T$ and 27.0% based on $K_1$. DSC was 0.87.

Figure 10.4. Correlation (left) and Bland-Altman (right) plots of defect size based on $MBF_T$ and $K_1$. The slope of the linear fit was 0.90, which was not significantly different from 1 ($p = 0.24$); intercept was 1.37, which was not significantly different from 0 ($p = 0.50$).
both infarcted and perfusable tissue) showed that $K_1$ significantly underestimated MBF$_T$, suggesting that the extraction of $[^{11}\text{C}]$HED is about 40–50%. Whilst this may hamper the use of $[^{11}\text{C}]$HED as an absolute myocardial blood flow tracer, the underestimation of $K_1$ was consistent over the range of MBF$_T$ observed in this study (i.e. extraction remained relative constant), as indicated by the significant correlation between $K_1$ and MBF$_T$ ($r^2=0.65, p<0.001$). As assessment of MBF-innervation mismatches zones is performed using relative cut-off values compared with remote control segments (58), a consistent underestimation of $K_1$ relative to MBF is expected to play a limited role. This was indeed confirmed in the present study, as the correlation of the defect sizes obtained with $K_1$ and MBF$_T$ was high ($r^2=0.91$). In addition, the slope of the linear fit was not significantly different from 1, Bland Altman analysis showed no significant differences between both defect sizes, and paired Wilcoxon rank tests showed no significant differences, indicating the potential of using $K_1$ instead of MBF$_T$ for mismatch assessment.

It is important to note that this study focused on the use of 50% of a healthy reference region as a cut-off value for both MBF$_T$ and $K_1$. As the optimal method for defining patient specific cut-off values is as yet unknown, a value of 50% may not be optimal. Therefore this study included relative cut-off values between 20 and 80% of the value of a healthy reference region (table 10.1). For 20-25% and for 75-80%, correlation was reduced to an $r^2$ below 0.80 and for cut-offs of 60% and higher, slopes of the linear fits without intercept started to deviate significantly from 1. However, for the range of 30-60%, both correlation coefficients and slopes were comparable with the results obtained when using a 50% cut-off value and for none of the assessed cut-off values, a significant difference was found using using paired Wilcoxon rank tests. This indicates that defect areas for $K_1$ and MBF$_T$ are similar for a wide range of relative

Figure 10.5. Correlation (left) and Bland-Altman plot (right) of mismatch size based on MBF$_T$ and $K_1$. The slope of the linear fit was 0.89 and not significantly different from 1 ($p = 0.32$). Intercept of the linear fit was 2.20 and was not significantly different from 0 ($p = 0.21$).
cut-off values for differentiating between healthy and defect tissue. In addition, for different cutoff values, average DSC for all patients was slightly lower at increased cut-offs. However, average DSC was above 0.80 for all cut-off values studied, except for 80%.

In this study, $^{11}$C]HED $K_1$ was compared with the product of MBF and PTF. This was performed since MBF derived from a $^{15}$O$\text{H}_2\text{O}$ scan represents MBF in perfusable tissue, whilst $^{11}$C]HED $K_1$ represents transmural rate of influx, i.e. in both perfusable and non-perfusable tissue within a region. Ideally, $^{11}$C]HED $K_1$ should be corrected for PTF in order to obtain $K_1$ in perfusable tissue only. This is, however, not possible without an additional $^{15}$O$\text{H}_2\text{O}$ scan and, therefore, transmural MBF (MBF$_T$) was used instead by multiplying MBF with PTF.

The results of this study are in contrast to those of Rimoldi et al (202), in which no correlation between MBF and $^{11}$C]HED $K_1$ was found in dogs. There are, however, two major differences between the two studies. First, in the present study, $^{11}$C]HED $K_1$ was compared with the product of MBF and PFI, i.e. transmural MBF, whilst the paper of Rimoldi et al. used regular MBF as obtained with $^{15}$O$\text{H}_2\text{O}$. Since MBF obtained with $^{15}$O$\text{H}_2\text{O}$ represents MBF in viable tissue only and $K_1$ represents HED influx in both viable and nonviable tissue, comparing MBF with $K_1$ may be inappropriate. To illustrate this, although still significant, in the present study the correlation between regular non-transmural MBF and $^{11}$C]HED $K_1$ was significantly lower with an $r^2$ of 0.45. Second, the range of MBF values in the present study was much larger than those of Rimoldi et al (31), as only patients with ischemic cardiomyopathy, and hence myocardial infarctions and large heterogeneities in MBF, were included. The dogs used in (202) showed regions of denervation but no infarctions and therefore, the range of MBF values was relatively small.

## 10.5 Conclusion

The rate of influx ($K_1$) of $^{11}$C]HED can be used as an alternative to a separate MBF scan when assessing mismatch zones between MBF and innervation in patients with ischemic cardiomyopathy. This reduces scan duration, radiation dose and risk of patient motion between scans.

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