Flow-dependent uptake of I-123-CMICE-013, a novel SPECT perfusion agent, compared to standard tracers

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Running Title: Flow-dependent uptake of CMICE-013
Abstract

Rotenone derivatives have shown promise in myocardial perfusion imaging (MPI). CMICE-013 is a novel I-123-labeled rotenone derivative developed for SPECT MPI. The objective of this study was to assess the image quality of CMICE-013 and compare its uptake to tetrofosmin, sestamibi and Tl-201 in vivo in a porcine model of stress-induced myocardial ischemia.

Methods: Microspheres were injected simultaneously with the radiotracer injections at rest and stress to measure blood flow. Mimicking a one-day tetrofosmin protocol, stress imaging used three times as much activity and occurred one hour after the rest injection. SPECT images were obtained at both rest and stress. Following imaging, the heart was sectioned into 44-50 pieces. In each heart sample, the tracer uptake was measured in a gamma counter. The images were aligned and the decay-corrected ratio of the signals at rest and stress was used to separate the well-counter signal into rest and stress components. The uptake at rest and stress were compared to microsphere flow measurements.

Results: The CMICE-013 images showed good contrast between the heart and surrounding organs with heart:liver and heart:lung uptake ratios similar to those of the standard tracers. Uptake of CMICE-013 was 1.5% of the injected dose (ID) at rest and increased more rapidly with increased blood flow than did the standard SPECT tracers. The %ID of CMICE-013 taken up by the heart was greater (p<0.05) than Tl-201, tetrofosmin or sestamibi at flows greater than 1.5 mL/min/g.

Conclusions: CMICE-013 is a promising new SPECT myocardial perfusion imaging agent.

Keywords: I-123-CMICE-013, Myocardial Perfusion Imaging, SPECT, microspheres
INTRODUCTION

Repeated unexpected shutdowns of several of the major nuclear reactors producing Mo-99 has led to ongoing concern over the stability of the supply of Tc-99m and, consequently, interest in developing alternative tracers. Myocardial perfusion imaging (MPI) remains one of the more common tests performed with Tc-99m-labeled agents. For MPI, PET is a potential option using either Rb-82 or N-13-ammonia, because the parent isotope for Rb-82 generators (Sr-82) and ammonia are both cyclotron produced. Interest in PET MPI is growing, however, the number of MPI SPECT scans performed annually in North America is still orders of magnitude larger and likely to remain so for many years. Thus, a SPECT alternative to Tc-99m MPI tracers remains an important goal.

Clinical trials of the F-18 labeled PET tracer flurpiridaz (1,2) have shown excellent contrast between the heart and surrounding organs and superior performance to standard Tc-99m-based tracers for the identification of disease. This tracer inhibits mitochondrial complex I (MC-I) and derives its specificity for cardiac imaging from the high concentration of mitochondria in the heart. Other compounds that target MC-I have been studied previously in SPECT. An iodinated rotenone compound (I-ZIROT) was shown to have excellent uptake in the heart and excellent extraction at higher blood flows (3,4). This is in contrast to the standard SPECT Tc-99m tracers that have a roll-off in their extraction, producing a plateau in tracer uptake, at flow-rates of 1.5-2x normal resting flow (5,6). The roll-off in extraction fraction limits the contrast between normal and abnormal tissues and can degrade the accuracy of MPI. Tl-201 also has good extraction at high flow rates. However, the long half-life of Tl-201 results in high patient radiodosimetry which limits the activity that can be injected and leads to noisy, poor quality images compared with Tc-99m tracers. An I-123-labeled rotenone derivative may provide the benefits of a good extraction fraction with improved imaging characteristics and dosimetry. I-123 emits 159 keV gamma rays, similar to the 140keV photon emission of Tc-99m and thus would be well suited to imaging with current gamma cameras. These factors led us to develop of a new SPECT MPI tracer based on an I-123-labelled rotenone derivative: CMICE-013.
The chemical structure and characterization of CMICE-013 has been published (7). CMICE-013 has a good toxicity profile (8) and initial biodistribution studies in rats demonstrated excellent uptake in the heart and contrast with surrounding organs. The effective dose of a 185MBq injection was estimated from preclinical studies to be 1.3-3.9 mSv (9,10). This study’s objectives were to assess the image quality of CMICE-013 and compare its uptake to tetrofosmin, sestamibi and Tl-201 in vivo in a porcine model of myocardial ischemia.

MATERIALS AND METHODS

Tracer Formulation

The formulation and chemical nature of CMICE-013 has been described (7). Whereas I-ZIROT replaced the 7'-carbon hydrogen of rotenone with iodine, I123-CMICE-013 adds an iodine to the 7'-carbon and reduces the 6',7'-double bond to a single bond with the addition of a hydroxy group at the 6'-position. Briefly, 12.5 mCi of NaI-123 solution in 0.1 M NaOH was mixed with 170 µL rotenone solution (2,5 mg/mL in trifluoroacetic acid (TFA)) and 30 µL iodogen solution (0.75 mg/mL in TFA). The mixture was heated at 60 °C for 45 min. After cooling to room temperature, the mixture was purified by reverse phase High Performance Liquid Chromatography (HPLC) with ethanol/water (48/52% v/v) as mobile phase. After evaporating the ethanol, the purified product was reconstructed in 5% ethanol in 10 mM NaOAc pH 6.5 as the final product for animal injection. The radiochemical purity of the final product was ≥ 95% as indicated by HPLC.

Tetrofosmin, sestamibi, and Tl-201 were acquired as unit doses from a commercial radiopharmacy (Cardinal Health Canada Nuclear Medicine Service).

Pig Model Preparation

We used a pig model of normal flow at rest and transient occlusion of the left-anterior descending artery (LAD) at stress to mimic stress-induced ischemia, similar to the approach used by Nekolla et al. (11).
This protocol was done in accordance with the guidelines of the Canadian Council on Animal Care and with approval from the Animal Care Committee at the University of Ottawa. Twenty-one 30-40 kg farm-bred Yorkshire cross female pigs successfully completed the protocol, 7 with CMICE-013, 5 with Tc-99m-tetrofosmin, 4 with Tc-99m-sestamibi and 6 with Tl-201. An additional group of 11 animals completed the protocol using a normal model (no occlusion) of rest/stress: 3 with CMICE-013, 4 with tetrofosmin, 1 with sestamibi and 2 with Tl-201. Animals were anaesthetized with Telazol and maintained using 2-3% isoflurane. For the ischemia model, a thoracotomy was performed and a suture loop placed around the LAD just below the second diagonal branch. Prior to closing the thoracotomy, suture lines were brought out of the chest allowing occlusion and release during imaging. Catheters were placed in the left atrium for microsphere injection, in the ear for tracer injection, in the opposite ear for fluids and dipyridamole, and in the femoral artery for blood withdrawal during microsphere measurements. For the normal model, the procedure was the same except that the suture loop was not placed around the LAD. The heart rate, blood pressure and body temperature of the animals were monitored throughout the experiment.

Imaging

Following surgery, the animals were maintained under anaesthetic and brought to the nuclear medicine imaging suite. The imaging protocol was similar to that of a one-day rest/stress Tc-99m-tetrofosmin protocol with a one-hour delay between rest and stress injections and approximately three times as much activity injected at stress as at rest. For CMICE-013, 74MBq (2mCi) were injected at rest and 222MBq (6 mCi) were injected at stress. The pigs were placed supine in a solid-state dedicated cardiac SPECT camera (Discovery NM 530c, GE Healthcare). Radiotracer and microsphere injections were started simultaneously. We used two different neutron-activated microspheres (BioPal Inc), gold at rest and samarium at stress. For each, blood was withdrawn for 4 min at 4 mL/min. Image data were acquired for 15 min starting just prior to tracer injection. A second 15 min image was acquired immediately following
and a third image acquired starting at 45min post-injection at rest. At one-hour after the rest injection, an infusion of dipyridamole (0.142 ug/kg/min over 4min) was started. Phenylephrine was given as needed to maintain blood pressure. For the ischemia model, 4 min after the end of the dipyridamole infusion, the suture was tightened and the LAD was occluded. Thirty seconds after occlusion, the stress tracer was injected concurrent with a second injection of microspheres. Two minutes after tracer injection, the occlusion was released. Two consecutive 15min stress images were acquired starting immediately after tracer injection. Only a brief period of ischemia was used to minimize infarction of the myocardium. For tetrofosmin and sestamibi imaging, the preparation and imaging procedure was the same except that 370 MBq (10 mCi) of tracer were injected at rest and 1100 MBq (30 mCi) at stress. For Tl-201, 37 MBq (1mCi) and 111 MBq (3mCi) were injected at rest and stress respectively. To minimize the effects of tracer redistribution, only one stress image was acquired for the Tl-201 protocol and the animal was euthanized immediately following the stress image. For the normal animals, the imaging procedure was the same excepting no occlusion of the LAD at stress.

The animal was euthanized with an injection of sodium pentabarbital immediately following completion of imaging. The heart was then extracted and rinsed. The left ventricle (LV) was isolated and sliced into 5 transverse slices of similar thickness. Each slice was divided into 1-2 g transmural segments resulting in 44-50 samples per heart. Samples were weighed and then measured in a NaI automated well-counter (Wizard3 2480, Perkin Elmer).

**Image processing**

Images were reconstructed using a vendor supplied iterative algorithm that includes collimator modeling and a noise-suppression prior. Similar to the recommended clinical protocol for Tc-99m-tracers, we used 40 iterations and a post-reconstruction 3D Butterworth filter (order 10, cut-off 0.37 cycles/cm) for all tracers. No attenuation or scatter correction was applied.
To assess CMICE-013 blood-pool clearance, images from 4 pigs were created every 30 s for the first 15 minutes following tracer injection at rest and stress. To evaluate image quality, the scans were divided into 5-minute intervals and the ratio of the maximum counts in the heart was compared to that of the liver and a lung volume-of-interest. Ratios were averaged over all animals for each tracer. Additional analysis is described in the supplemental material.

The last rest image, acquired immediately prior to the stress infusion, and the last stress image were imported into Matlab-based software and the hearts in each image were coregistered manually using rigid-body translation. The heart image was segmented in 3D to match the sectioning of the extracted heart into tissue samples. Polar map representations of the sampled heart for the well-counter measurements and the stress image were then compared to confirm the alignment of the tissue samples with the images. For each sample, the fraction of counts associated with the rest injection was determined by first decay correcting the resting image to the time of the stress image acquisition. The summed counts in each sample from the rest image was then divided by the counts in the corresponding stress image sample to calculate the rest fraction. The decay correction of the rest image included correction for both radioactive decay of the isotope and biological clearance of the tracer. The biological clearance of sestamibi was taken to be 355 min (t/2). The clearances of the other tracers were found using the three acquired rest images from 5 animals for each tracer. The listmode data from these acquisitions were rebinned into 5 min intervals and independently reconstructed. The first image following injection was not used due to the presence of blood-pool activity. For each pig, the heart image was manually segmented, the total counts in the heart was determined and then normalized to the counts in the first image. The data for all 5 pigs were pooled. Assuming a mono-exponential biological clearance, the log of the heart counts were corrected for physical decay and fit to a straight line as a function of time to find the biological half-life.

The rest- and stress-fractions, where the stress fraction equaled 1 minus the rest fraction, were applied to the well-counter measurements to separate these into rest and stress components. The rest and stress
well-counter measurements were then converted into a percent of injected activity per gram of heart tissue.

**Microsphere Blood Flow Comparison**

The microspheres in each tissue sample and blood reference samples were measured by BioPAL Inc. The signal in each sample was then converted into a measurement of blood flow using standard methods (13):

\[
MBF = 4 \text{ mL/min} \times \frac{\text{counts in sample}}{(\text{counts in blood}) \times \text{tissue weight}}
\]

Eq. 1

Similar to the work by Glover et al. (5,6), the tissue uptake was fit to the microsphere measurements of blood flow using Eq. 2 which represents a scaled Renkin-Crone model of the extraction fraction.

\[
PID = a_3 \times MBF \times \left\{1 - e^{-\left(a_1 + \frac{a_2}{MBF}\right)}\right\}
\]

Eq. 2

where PID is the percent injected dose per gram of tissue sample, MBF is the myocardial blood flow measured by microspheres, and \(a_i\) are the fitted parameters.

Fits were calculated for each individual animal using non-linear least-squares optimization applied to the combined rest and stress values and also for the aggregate data from all animals injected with the same tracer. Quality of the fits was indicated by the coefficients of determination (\(r^2\)). Uptake in the heart at a selection of flow rates was estimated from the fits to the aggregate data and compared to standard tracers with a t-test using uncertainties estimated from the standard deviations of the individual animal fits. Summary data are presented as mean +/- standard deviation and a p-value of 0.05 or less was considered significant.

**RESULTS**

Heart rate and systolic blood pressure in the animals was similar for all tracers (Table 1). The biological half-lives of the tracers in the heart were found to be 217 min for Tl-201 and 330 min for tetrofosmin, and
1005 min for CMICE-013. The coefficients of determination for Tl-201, tetrofosmin and CMICE-013 were 0.69, 0.54, and 0.37 respectively. The blood time-activity curves (TAC) of CMICE-013 at rest and stress (Figure 1) show good clearance of the tracer within 5min post-injection. Representative transverse, sagittal and coronal images of the CMICE-013 tracer distribution (Figure 2) show the good contrast between the uptake in the heart and that in the surrounding tissues. Averaged CMICE-013 time-activity curves of the heart:liver and heart:lung ratios (Figure 3) are similar to the standard SPECT tracers. Cardiac (short-axis, vertical long axis, and polar map) views (Figure 4) of the tracer distribution demonstrate good uniformity at rest and a clear definition of the occluded region during stress. Serial imaging showed that CMICE-013 does not redistribute rapidly (Supplementary Figure S5 and Table S1). Finally, compared to microsphere measured myocardial blood flow, we see that the CMICE-013 tracer has a greater %ID/g uptake at rest, increases linearly with stress, and increases at a more rapid rate than do the standard SPECT perfusion tracers (Figure 5) producing a significantly increased myocardial uptake (Table 2).

DISCUSSION

The images of CMICE-013 (Figures 1-4) show good imaging characteristics. Blood pool clearance is rapid, with most of the tracer cleared in the first 3 minutes (Figure 1). The contrast between the heart and lungs is excellent (Figures 3,4) – the contrast for CMICE-013 is higher than Tl-201 but lower than sestamibi and similar to tetrofosmin. The heart to liver contrast is similar to the standard SPECT tracers (Figures 3,4). The occluded territory is clearly seen in the stress images (Figures 2,4) with good contrast between low-flow and high-flow regions.

The uptake of CMICE-013 increases more rapidly with increased blood flow than all three of the standard SPECT perfusion tracers and has a higher percentage uptake per gram of myocardial tissues over the full range of blood flow values measured (Figure 5). This suggests that CMICE-013 will have a larger percentage uptake in the heart, leading to a stronger signal and less noise in the cardiac images. The
larger slope means that it would also have better contrast between regions of low and high flow. This could improve the sensitivity of the tracer for detecting regions of abnormal perfusion, particularly under high-flow conditions. This behavior is similar to other perfusion compounds (Figure 5) that, like rotenone, bind to mitochondrial complex I: I-123-iodorotenone (ZIROT) (3) and 18F-flurpiridaz (14). For the purpose of comparison, the relative uptake curve for I-ZIROT (3) was scaled to match the absolute uptake for CMICE-013 at a microsphere flow of 1 mL/min/g.

Based on fitted value for the uptake versus flow curve of the tracers, an average uptake in the heart was calculated (Table 2). The average LV weight was 70g and the average resting microsphere-measured blood flow was 0.9mL/min/g. This gives an uptake of 1.8 % of the injected dose (ID) at rest for CMICE-013. A stress flow of 2 mL/min would yield an uptake of 2.4 %ID. In comparison, the tetrofosmin uptake was measured as 1.1% at rest and 1.2% at a flow of 2mL/min whereas sestamibi had uptakes of 1.4% and 1.7% at the same flow rates. These values are consistent with estimates of percent tracer uptake at rest and stress from previous studies (15,16) and suggest that CMICE-013 may have greater myocardial uptake than currently used Tc-99m tracers. The uptake of Tl-201 was more linear with flow than were the Tc-99m-tracers, but also had lower %ID uptake in the heart: 1.2% at 0.9 mL/min/g and 1.5% at 2.0 mL/min/g.

One limitation of our approach is tracer redistribution. Because the animal is not terminated for ~60 min after rest imaging and ~30min after stress, redistribution of the tracer in that time may distort our estimates of the relative fraction of activity in the tissue sample. We have corrected for global biological clearance from the heart, but redistribution could additionally change the spatial distribution of tracer in the heart muscle. Redistribution of Tl-201 is known to be rapid, requiring stress imaging within 10-15min post-injection. A washout of the rest tracer would serve to decrease the true rest fraction compared to that estimated from the images. Redistribution would also serve to fill in the reduced uptake in the transiently occluded region, reducing the apparent contrast. In the case of Tl-201, effort was made to minimize this effect by sacrificing the animal immediately following the end of the first stress image (15min post-stress
injection). CMICE-013, like the standard Tc-99m-tracers sestamibi and tetrofosmin, does not rapidly redistribute (supplementary materials). An additional limitation of this model is that brief periods of ischemia can produce hyperemia following reperfusion (17). Any residual or redistributed tracer in the blood following reperfusion will be taken up in the ischemic area in proportion to an elevated flow rate and this would also increase uptake. The amount of tracer in the blood at reperfusion is small (Figure 1), but we note that the tissue samples with very low microsphere flow have non-zero uptake leading to a non-zero intercept in the fitted line. Redistribution and residual tracer in the blood after reperfusion may be a contributing factor to the uptake seen in the very-low-flow samples.

Attenuation and scatter corrections were not applied during the reconstruction of the images. Attenuation is known to cause artifacts in cardiac images, altering the relative distribution (18,19). In our study, though, the uptake of the CMICE tracers is measured using a well-counter and the self-attenuation in the 1-2g samples should be negligible. The fraction corresponding to rest is estimated from the ratio of the rest and stress images. In this ratio, the effects of attenuation will cancel out as the animal remains in the same position in the camera throughout imaging. It is not as clear that the effects of scatter will cancel as the distribution of activity can change from stress to rest causing a change in the scatter fraction. In addition, scatter serves to reduce the contrast in areas of reduced uptake and this could serve to alter the ratio of rest to stress counts. The vendor reconstruction software used for this study did not allow correction for scatter. Scatter correction would have to be applied as a pre-correction to the projection data offline and the corrected projections loaded back onto the camera for reconstruction. While possible, this approach was not pursued for this study. Thus scatter could also be one of the contributing factors to the non-zero uptake seen in low-flow regions with both tracers.

Finally, partial volume effects caused by the limited resolution of the scanner and the post-filtering will also blur the estimated rest fraction of activity. Although the well-counter measurements are not affected by the spatial resolution of the images, the limited spatial resolution will cause spill-in of counts into the region of the transient occlusion and thus reduce apparent contrast at stress. This will in turn increase the
apparent fraction of counts associated with stress and could lead to increased values for the uptake in the occluded region.

A final limitation of this study is that the biodistribution of the tracer was not measured. As with all iodinated radiotracers, de-iodination in vivo will occur with this tracer which would lead to accumulation in and significant radiation exposure to iodine-avid organs such as the thyroid. Biodistribution measurements of CMICE-013 in rats (9) estimate a patient radiation exposure of 7 μSv/MBq and preliminary studies in separate pigs (10) estimate 21μSv/MBq. These are similar to other I-123 SPECT tracers and, like these other tracers, a thyroid blocking agent administered prior to MPI imaging would be recommended to minimize uptake. A thorough evaluation of CMICE-013 biodistribution in pigs will be reported separately, although more clinically-relevant dose estimates will require evaluation in human volunteers.

CONCLUSION

A novel I-123-labeled SPECT myocardial perfusion imaging tracer, CMICE-013, has been studied in a pig model of stress-induced ischemia. The tracer has good contrast between the heart and surrounding organs. CMICE-013 has greater myocardial uptake compared to TI-201, Tc-99m-sestamibi and Tc-99m-tetrofosmin and it displays a greater, more linear change in uptake with increased blood flow. CMICE-013 is a promising new non-Tc-99m-tracer for SPECT MPI.
FUNDING SOURCES

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DISCLOSURES

RG Wells and TD Ruddy collaborate with GE Healthcare and have received research support. L Wei, Y Duan, P Fernando, and C Bensimon were employees of Nordion Inc during this study.
REFERENCES


Figure 1: Blood time-activity curve for CMICE-013 based on counts from a volume of interest in the left ventricle. The time-activity curves do not go to zero at late times due to the limited spatial resolution of SPECT and consequent spill-in from tracer in the myocardial wall.
Figure 2: Representative CMICE-013 images of a porcine model of stress-induced myocardial ischemia showing stress (top row) and rest (bottom row) from 15-30min post-injection. Images are central slices in the transverse (A,D), coronal (B,E) and sagittal (C,F) views. Images show good contrast between the heart and surrounding tissues except for the liver whose contrast is similar to that of standard SPECT tracers.
Figure 3: Ratios of maximum uptake in the heart compared to the liver and lung at rest (A) and stress (B) for each of the tracers studied.
Figure 4: Representative CMICE-013 images of the heart. Images are shown at rest and stress (both 15min post-injection) presenting the short axis (top two rows), vertical long axis (middle two rows) and polar maps of the tracer distribution. The images show good uniformity at rest and a clear definition of the occluded region during stress.
Figure 5: Tracer uptake versus microsphere flow values for each tissue sample from the individual animals with CMICE-013 (A), Tc-99m-tetrofosmin (B), Tc-99m-sestamibi (C), thallium-201 (D). The
fit to Eq. 2 is shown as a solid line for each data set with the 95% confidence interval on the fit represented by dotted lines. Legend entries indicate normal (n) or ischemic (i) pigs. The fitted curves to the combined data are replotted separately for clarity (E) along with a curve derived from previously reported data for I-123-iodorotenone (ZIROT) (3) as described in Supplementary Methods.
Table 1: Heart rate and systolic blood pressure for the animals at rest and stress.

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Rest HR (bpm)</th>
<th>Rest SBP (mm Hg)</th>
<th>Stress HR (bpm)</th>
<th>Stress SBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMICE-013</td>
<td>82 ± 12</td>
<td>66 ± 10</td>
<td>82 ± 10</td>
<td>59 ± 4</td>
</tr>
<tr>
<td>(n=10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrofosmin</td>
<td>84 ± 8</td>
<td>71 ± 8</td>
<td>86 ± 5</td>
<td>63 ± 9</td>
</tr>
<tr>
<td>(n=9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sestamibi</td>
<td>83 ± 11</td>
<td>66 ± 18</td>
<td>83 ± 14</td>
<td>60 ± 16</td>
</tr>
<tr>
<td>(n=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TI-201 (n=8)</td>
<td>88 ± 11</td>
<td>69 ± 11</td>
<td>92 ± 8</td>
<td>60 ± 8</td>
</tr>
</tbody>
</table>

bpm = beats per minute
Table 2: Left ventricular heart uptake (%ID/g x 70g*) at selected microsphere flow values.

<table>
<thead>
<tr>
<th>Microsphere flow (mL/min/g)§</th>
<th>Tracer</th>
<th>0.9†</th>
<th>1.5</th>
<th>2.0</th>
<th>3.0</th>
<th>4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMICE-013</td>
<td></td>
<td>1.8</td>
<td>2.1</td>
<td>2.4</td>
<td>2.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Tetrofosmin</td>
<td></td>
<td>1.1‡</td>
<td>1.1‡</td>
<td>1.2‡</td>
<td>1.2‡</td>
<td>1.3‡</td>
</tr>
<tr>
<td>Sestamibi</td>
<td></td>
<td>1.4‡</td>
<td>1.6‡</td>
<td>1.7‡</td>
<td>1.8‡</td>
<td>1.9‡</td>
</tr>
<tr>
<td>Tl-201</td>
<td></td>
<td>1.2‡</td>
<td>1.3‡</td>
<td>1.5‡</td>
<td>1.8‡</td>
<td>2.1‡</td>
</tr>
</tbody>
</table>

* The heart weight used (70g) is the average LV weight of the pig hearts in this study.

§ Flow values based on fit for aggregate data to Eq. 2.

† 0.9 mL/min/g is the average pig resting microsphere flow.

‡ significantly different from CMICE-013 (p<0.05)
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