

# Motion-corrected imaging of the aortic valve with $^{18}\text{F}$ -NaF PET/CT and PET/MR: a feasibility study

Mhairi K. Doris, MD <sup>1,2\*</sup>, Mathieu Rubeaux, PhD <sup>1\*</sup>, Tania Pawade <sup>2</sup>, MD, Yuka Otaki, MD<sup>1</sup>, Yibin Xie, PhD<sup>3</sup>, Debiao Li, PhD<sup>3</sup>, Balaji K. Tamarappoo, MD, PhD <sup>1</sup>, David E Newby, MD<sup>2</sup>, Daniel S. Berman, MD<sup>1</sup>, Marc R Dweck, MD<sup>2</sup>, Piotr J. Slomka, PhD<sup>1</sup>, Damini Dey, PhD<sup>3</sup>.

<sup>1</sup> Departments of Imaging and Medicine, Cedars-Sinai Medical Center, Los Angeles, California

<sup>2</sup> Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom

<sup>3</sup> Biomedical Imaging Research Institute, Cedars-Sinai Medical Center, Los Angeles, California

\* Equally contributing authors

## Corresponding Author

Damini Dey, PhD

Biomedical Imaging Research Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Taper, Suite A238

Los Angeles, CA 90048, USA

Tel: 310-423-1517

Fax: 310-423-8396

[damini.dey@cshs.org](mailto:damini.dey@cshs.org)

## First Authors

Mhairi K Doris, MD

Department of Imaging and Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd Los Angeles, CA 90048, USA

[Mhairi.doris@cshs.org](mailto:Mhairi.doris@cshs.org)

Mathieu Rubeaux, PhD, fellow

Artificial Intelligence in Medicine Program, 8700 Beverly Blvd, Suite A047N

Los Angeles, CA 90048, USA

[mathieu.rubeaux@cshs.org](mailto:mathieu.rubeaux@cshs.org)

Running title: Aortic valve imaging with  $^{18}\text{F}$ -FluoridePET (40 characters with spaces max)

**Word count: 2497/2500 (abstract 149)**

## ABSTRACT

**Introduction.** We investigated whether motion correction of gated  $^{18}\text{F}$ -fluoride PET-CT and PET-MR of the aortic valve could improve PET quantitation and image quality.

**Methods.** A diffeomorphic, mass-preserving, anatomy-guided registration algorithm was used to align PET images from 4 cardiac gates, preserving all counts, and applied to PET-MR and PET-CT data of six patients with aortic stenosis. Measured Signal-to-Noise Ratios (SNRs) and Target-to-Background Ratios (TBRs) were compared with the standard method of utilizing only the diastolic gate.

**Results.** High-intensity aortic valve  $^{18}\text{F}$ -fluoride uptake was observed in all patients. Following motion correction, SNR and TBR increased compared to the diastolic gate (SNR 51.61 vs 21.0; TBR 2.85 vs 2.22) and summed data (SNR 51.61 vs 34.10; TBR 2.85 vs 1.95, median,  $p=0.028$  for all). Furthermore, noise decreased from 0.105 (median, diastolic) to 0.042 (median, motion-corrected [ $p=0.028$ ]).

**Conclusions.** Motion-correction of hybrid  $^{18}\text{F}$ -fluoride PET markedly improves SNR, resulting in improved image quality.

**Keywords:**  $^{18}\text{F}$ -Fluoride, PET-MR, PET-CT, motion correction, aortic stenosis.

## INTRODUCTION

Aortic stenosis is the commonest form of valve disease in the western world and is set to increase rapidly with an aging population (1,2). Recently, interest has developed in the potential role of  $^{18}\text{F}$ -fluoride Positron Emission Tomography (PET) for the assessment of disease activity, the prediction of disease progression and as an end point in clinical trials investigating novel therapies (2,3).

Combined PET Computed Tomography (PET-CT) and PET Magnetic Resonance (PET-MR) each possess unique attributes suited to the assessment of aortic stenosis. PET-CT provides detailed anatomical information with respect to valve morphology and calcification and may allow for the assessment of calcification in bioprosthetic valves, while PET-MR informs about the hypertrophic response of the left ventricle, myocardial fibrosis and the transition to heart failure (4).

A major challenge faced in PET-CT and PET-MR imaging of the heart is the impact of cardiac, respiratory and gross patient movement on PET image quality. Prior  $^{18}\text{F}$ -fluoride PET-CT studies have utilized PET data reconstructed from the end-diastolic phase only (25% of total PET counts) to avoid blurring from cardiac motion, but at the expense of increased image noise (5,6). We have developed a novel software cardiac motion correction method which allows the use of data from the full cardiac cycle and we have recently demonstrated that this method enhances image quality and quantitation in the coronary arteries while reducing noise (7). To our knowledge, this approach has not yet been applied to patients with valvular heart disease nor PET-MR imaging. In this dual center study, we report the use of multimodality motion correction in hybrid PET-CT and PET-MR in a group of patients with aortic stenosis.

## MATERIALS AND METHODS

### Study Population

*PET-CT.* Patients with aortic stenosis were recruited prospectively from outpatient clinics at the Edinburgh Heart Centre as part of the ongoing SALTIRE 2 clinical trial (NCT02132026). The study was approved by the local research ethics committee in accordance with the declaration of Helsinki and all patients provided written informed consent.

*PET-MR.* A 60-year-old asymptomatic male was prospectively recruited as part of an ongoing research study. The study was approved by the IRB and the patient provided written informed consent for use of the data.

## **Image Acquisition and Analysis**

*PET-MR.* The PET-MR protocol involved PET acquisition in list mode for 40-60 min, with concurrent MR acquisitions to assess the myocardium comprehensively (Biograph mMR scanner, Siemens). These included standard cine views to evaluate left ventricular function, contrast-enhanced MR angiography acquired in diastole, late gadolinium enhancement for assessment of midwall fibrosis or infarction (8,9) and a new interleaved T1-weighted sequence ('CATCH') (10). The pre-contrast CATCH sequence facilitates acquisition of a dark-blood T1-weighted image in one heartbeat followed by an anatomical bright-blood reference in the next; post-reconstruction, a hyper-intense signal has been shown to correspond to thrombus or potential intra-plaque hemorrhage (10).

For PET-MR imaging, 212 MBq of  $^{18}\text{F}$ -fluoride was injected and MR image acquisition began 20 min later. PET acquisition began one hour post injection and was performed in list mode for over 60 min. Dixon-based MR images for water and fat were used for attenuation correction using the standard method provided on the scanner.

*PET-CT.* 125 MBq of 18F-fluoride was administered intravenously and patients were subsequently rested in a quiet environment. After 60 min, image acquisition was performed using a hybrid PET-CT scanner (Biograph mCT; Siemens). Attenuation-correction CT scans were performed before acquisition of PET data in list mode using a single 30-min bed position centered on the valve in 3-dimensional mode. Finally, prospectively-ECG-gated contrast-enhanced CT angiography was performed in end-expiration. Patients were given 25 mg of oral metoprolol if their resting heart rate was >65 beats/min.

For both PET-MR and PET-CT, PET images were reconstructed using a standard iterative Ordered Subsets Expectation Maximization algorithm with resolution recovery (11), using 4 cardiac gates.

### **Cardiac Motion Correction**

Cardiac motion correction was performed using an anatomically-guided automated registration algorithm, similar to our method described previously (7, 12). First, a three-dimensional sphere was drawn to define the aortic valve region. A non-linear registration algorithm, radially constrained around the aorta and coronary tree centerlines, was used to align PET images to the diastolic gate. The non-linear registration algorithm used was a diffeomorphic, mass-preserving, anatomy-guided Demons method which optimizes the global energy between PET frames; with built-in optimization for anatomical data (13, 14). The motion corrected gates were then summed to form a motion-free image (12) containing all the PET counts. The motion correction procedure required approximately 10 min per patient. PET quantification was performed by delimiting 3-dimensional regions-of-interest on fused PET-MR angiography and PET-CT angiography using FusionQuant software (Cedars-Sinai Medical Center, Los Angeles, CA). For each PET-CT subject, rigid registration was performed between the PET data and CTA on the axial, sagittal and coronal planes using CTA data from the most optimal diastolic phase. For the PET-MR subject, MR angiography was acquired during a single diastolic phase and this image was similarly fused and manually registered with the PET data. Background blood pool activity was measured

in the right atrium using mean standardized uptake values from 3-dimensional spherical volumes.

Maximum uptake in the aortic valve was computed by creating a sphere-shaped volume of interest through the aortic valve after re-orientation of the image into the aortic valve plane (6). SNR (defined as the maximum uptake in the aortic valve divided by the image noise) and TBR (defined as the maximum uptake in the aortic valve divided by the mean standardized uptake value of the blood pool) values were computed in the motion-corrected image, summed image and in the original diastolic gate. PET image noise was calculated as the standard deviation of the blood pool measurement.

## Statistical Analysis

Statistical analyses were performed with SPSS (SPSS version 22, IBM corp, USA). Continuous variables were tested for normality and non-parametric data are expressed as median and interquartile range as appropriate. Two-sample *t*-test or Wilcoxon rank-sum test were applied to compare groups for continuous variables. A two-sided  $p < 0.05$  was taken as statistically significant.

## RESULTS

Increased  $^{18}\text{F}$ -NaF uptake in the aortic valve was observed in all six patients (Table 1 and Figures 1 and 2). Following motion correction, there was an increase in SNR and TBR when compared to the diastolic gate (SNR 51.61[32.79-61.15] vs 21.0 [16.37-25.25]; TBR 2.85[2.45-3.84] vs 2.22 [1.94-3.29], median [IQR],  $p=0.028$  for all) and summed data (SNR 51.61[32.79-61.15] vs 34.10[24.36-42.54]; TBR 2.85[2.45-3.84] vs 1.95[1.75-2.66], median[IQR],  $p=0.028$  for all) (Figure 3). Further, there was a reduction in noise in the motion corrected image when compared to both the summed data (0.042[0.037-0.076] vs 0.052[0.051-0.104]) and original diastolic gate (0.042[0.037-0.076] vs 0.105[0.096-0.160], median[IQR]  $p=0.028$  for all) (Figure 4). On the PET-MR scan, detailed CMR investigation of the left ventricle was possible including measurements of the left ventricle mass volumes ( $45 \text{ g/m}^2$ ) and ejection fraction (53%) as well as late gadolinium enhancement imaging. The CATCH sequence was also well tolerated by

the patient but did not reveal evidence of T1 hyperintense lesions in either the valve or the coronary arteries.

## DISCUSSION

This feasibility study represents the first analysis of multimodality cardiac motion correction guided by anatomical data from  $^{18}\text{F}$ -fluoride PET-MR and PET-CT. It also represents the first demonstration of hybrid PET/MR imaging in aortic stenosis which allows simultaneous imaging of calcification activity in the aortic valve using  $^{18}\text{F}$ -fluoride PET alongside the detailed myocardial assessments provided by MR.

In the future, this sophisticated imaging method has great clinical potential in assessing native aortic valve disease alongside markers of myocardial decompensation including midwall late gadolinium enhancement (8) and T1 mapping (15,16). However, a limitation of PET-MR is the inability to accurately assess prosthetic valve disease due to the influence of metal artifact on PET attenuation and MR image quality. With the increasing use of Transcatheter Aortic Valve Replacement (TAVR), PET-CT is likely to play an important role in the assessment of aortic valve bioprostheses. Indeed, the role of  $^{18}\text{F}$ -fluoride PET-CT in assessing the longevity of TAVR valves is currently under investigation (NCT02304276). Here, we describe how these imaging techniques may be optimized with motion-corrected imaging of the aortic valve to maximize the research and clinical potential of hybrid cardiac imaging.

Our study is limited by data from only a small number of patients. While this was sufficient to demonstrate the clear improvements in SNR and TBR values offered by motion correction techniques, larger studies are required for confirmation.

## CONCLUSION

Simultaneous motion-corrected PET imaging of the aortic valve is feasible with both hybrid  $^{18}\text{F}$ -fluoride PET-MR and PET-CT. Motion correction, using a diffeomorphic mass-preserving image registration algorithm, improved quantitative SNR and TBR while significantly reducing image noise.

## DISCLOSURES

No current conflict of interest related to this work.

## ACKNOWLEDGMENTS

The study was supported by a grant (*Cardiac Imaging Research Initiative*) from the Adelson Medical Research Foundation. The study was also funded by the British Heart Foundation (FS/14/78/31020; RG/16/10/32375) and Chief Scientist Office, Scotland (ETM/160). DN (CH/09/002) and MRD (FS/14/78) are supported by the British Heart Foundation. David Newby is the recipient of a Wellcome Trust Senior Investigator Award (WT103782AIA).

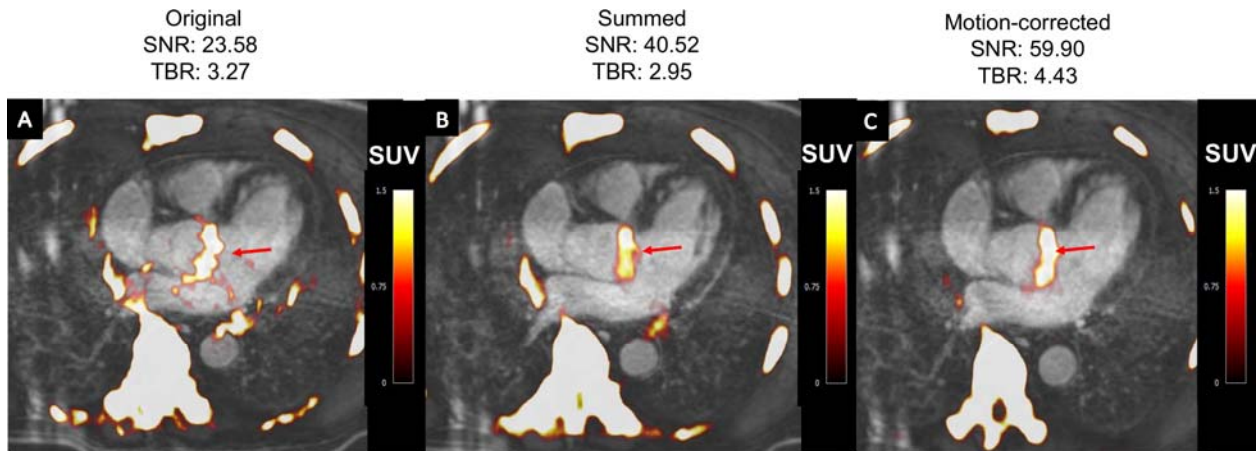


## REFERENCES

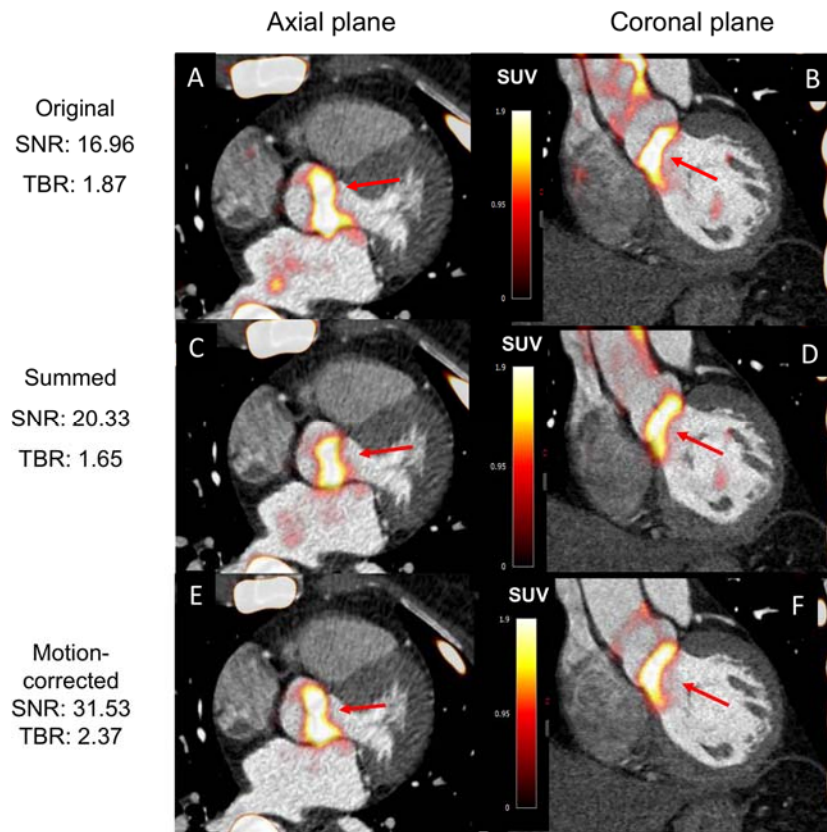
1. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. *J Am Coll Cardiol*. 2012;60:1854–63.
2. Pawade TA, Newby DE, Dweck MR. Calcification in aortic stenosis: the skeleton key. *J Am Coll Cardiol*. 2015;66:561–77.
3. Dweck MR, Jenkins WSA, Vesey AT, et al. 18F-sodium fluoride uptake is a marker of active calcification and disease progression in patients with aortic stenosis. *Circ Cardiovasc Imaging*. 2014;7:371–8.
4. Chin CWL, Pawade TA, Newby DE, Dweck MR. Risk stratification in patients with aortic stenosis using novel imaging approaches. *Circ Cardiovasc Imaging*. 2015;8:e003421.
5. Joshi NJ, Vesey AT, Williams MC, et al. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. *Lancet*. 2014;383:705–13.
6. Pawade TA, Cartlidge TRG, Jenkins WSA, et al. Optimization and reproducibility of aortic valve 18F-fluoride positron emission tomography in patients with aortic stenosis. *Circ Cardiovasc Imaging*. 2016;9:e005131.
7. Rubeaux M, Joshi N, Dweck MR, et al. Motion correction of 18F-sodium fluoride PET for imaging coronary atherosclerotic plaques. *J Nucl Med*. 2016;57:54-9.
8. Dweck MR, Joshi S, Murigu T, et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. *J Am Coll Cardiol*. 2011;58:1271–9.
9. Vassiliou VS, Perperoglou A, Raphael CE, Joshi S, Malley T, Everett R, et al. Midwall fibrosis and 5-year outcome in moderate and severe aortic stenosis. *J Am Coll Cardiol*. 2017;69:1755–6.
10. Xie Y, Kim Y-J, Pang J, et al. Coronary atherosclerosis T1-weighted characterization with integrated anatomical reference: comparison with high-risk plaque features detected by invasive coronary imaging. *JACC Cardiovasc Imaging*. 2016;doi: 10.1016/j.jcmg.2016.06.014. [Epub ahead of print]
11. Le Meunier L, Slomka PJ, Dey D, et al. Enhanced definition PET for cardiac imaging. *J Nucl Cardiol*. 2010;17:414–26.
12. Rubeaux M, Pawade T, Cartlidge T, et al. Cardiac motion compensation improves reproducibility of 18F-sodium fluoride PET uptake quantification in the aortic valve. *J Nucl Med*. 2016;57(supplement 2):506.
13. Vercauteren T, Pennec X, Perchant A, Ayache N. Symmetric log-domain diffeomorphic Registration: a demons-based approach. *Med Image Comput Comput Assist Interv*. 2008;11(Pt 1):754-761.

14. Rubeaux M, Joshi N, Dweck MR, et al. Demons versus Level-Set motion registration for coronary (18)F-sodium fluoride PET. Styner MA, Angelini ED, eds. *Proc SPIE Int Soc Opt Eng*. 2016;9784:97843Y–97843Y–7. doi:10.1117/12.2217179.
15. Chin CW, Everett RJ, Kwiecinski J, et al. Myocardial fibrosis and cardiac decompensation in aortic stenosis. *JACC Cardiovasc Imaging*. 2016; doi: 10.1016/j.jcmg.2016.10.007. [Epub ahead of print].
16. Everett RJ, Stirrat CG, Semple SIR, Newby DE, Dweck MR, Mirsadraee S. Assessment of myocardial fibrosis with T1 mapping MRI. *Clin Radiol*. 2016;71:768–78.

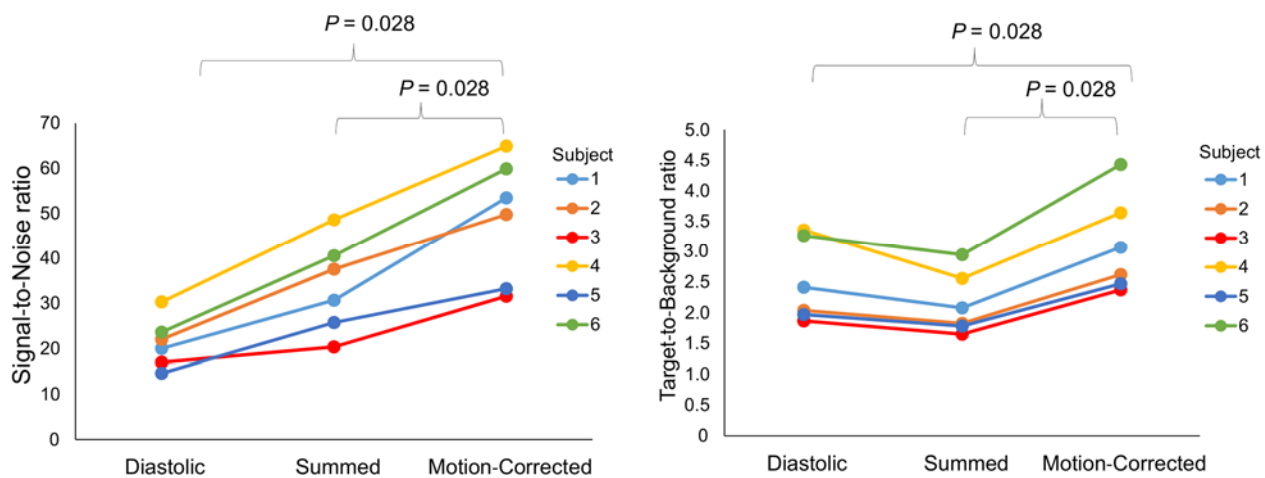
**Figure 1.** Fused  $^{18}\text{F}$ -fluoride PET and contrast-enhanced magnetic resonance angiography of the aortic valve in a 60-year-old male with aortic stenosis. Images display the original diastolic gate (A), summed image (B) and motion-corrected image (C) with focal  $^{18}\text{F}$ -fluoride uptake (red arrows).



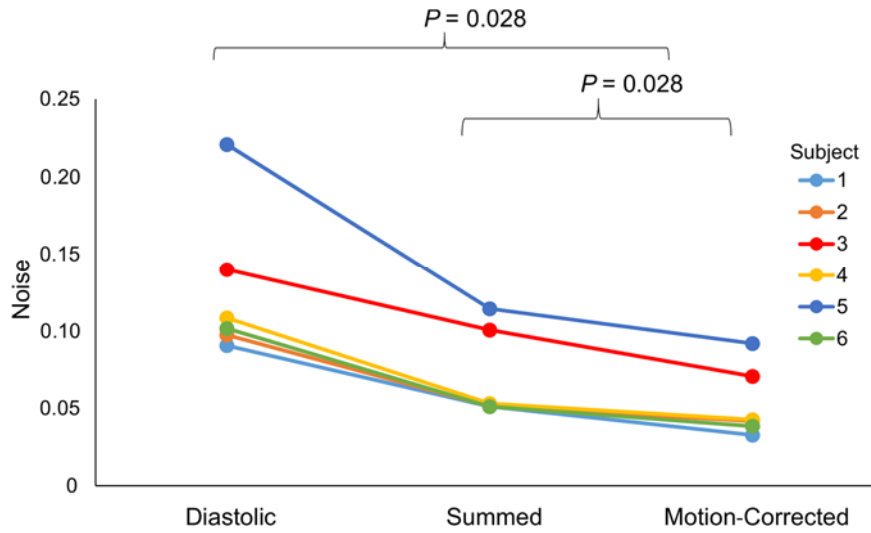
**Figure 2.** Fused PET-CTA images in a 79-year-old female with aortic stenosis. Images display the original diastolic gate (A -B), summed image (C-D) and motion-corrected image (E-F) demonstrating focal  $^{18}\text{F}$ -fluoride uptake (red arrows).



**Figure 3.** Signal-to-noise ratios (A) and Target-to-background Ratios (B) in original gate, summed and motion corrected data. NEW



**Figure 4.** Difference in noise between motion corrected image, original diastolic gate and summed image. While noise was higher in subjects 1 and 3, likely due to an increased body weight, the same trend was observed. NEW



**Table 1. Baseline Characteristics**

<b>Baseline Characteristics</b>	
Age in years, mean (SD)	74 (9)
Men, n (%)	4 (67)
Body Mass Index (kg/m <sup>2</sup> ), mean (SD)	27 (5)
<b>Past Medical History</b>	
CABG/PCI, n (%)	2 (33)
Previous MI, n (%)	0
Hypercholesterolemia, n (%)	4 (67)
Hypertension, n (%)	2 (33)
Renal Disease, n (%)	0
Diabetes, n (%)	2 (33)
<b>Medications</b>	
ACE inhibitors/AIIRB, n (%)	3 (50)
Beta blockers, n (%)	3 (50)
Statin, n (%)	4 (67)
<b>Echocardiography</b>	
AV jet velocity (m/sec), mean (SD)	3.23 (0.37)
AV mean gradient (mmHg), mean (SD)	24 (6.72)