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DOI:

[10.1002/mrm.27354](https://doi.org/10.1002/mrm.27354)

*Document Version*

Peer reviewed version

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*Citation for published version (APA):*

Bustin, A., Ginami, G., Cruz, G., Correia, T., Ismail, T. F., Rashid, I., Neji, R., Botnar, R. M., & Prieto, C. (2018). Five-minute whole-heart coronary MRA with sub-millimeter isotropic resolution, 100% respiratory scan efficiency, and 3D-PROST reconstruction. *Magnetic Resonance in Medicine*, [MRM27354].  
<https://doi.org/10.1002/mrm.27354>

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1           **Five-Minute Whole-Heart Coronary MRA with Sub-**  
 2           **millimeter Isotropic Resolution, 100% Respiratory Scan**  
 3           **Efficiency and 3D-PROST Reconstruction**

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 21   Short Title: Five-minute sub-millimeter CMRA with PROST  
 22   Submitted as Full Paper to Magnetic Resonance in Medicine  
 23   Word count: 4963  
 24

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## ABSTRACT

35  
36 **Purpose:** To enable whole-heart three-dimensional (3D) coronary magnetic resonance  
37 angiography (CMRA) with isotropic sub-millimeter resolution in a clinically feasible scan  
38 time by combining respiratory motion correction with highly accelerated variable density  
39 sampling in concert with a novel 3D patch-based undersampled reconstruction (3D-  
40 PROST).

41 **Methods:** An undersampled variable density spiral-like Cartesian trajectory was  
42 combined with 2D image-based navigators to achieve 100% respiratory efficiency and  
43 predictable scan time. 3D-PROST reconstruction integrates structural information from  
44 3D patch neighborhoods through sparse representation, thereby exploiting the redundancy  
45 of the 3D anatomy of the coronary arteries in an efficient low-rank formulation. The  
46 proposed framework was evaluated in a static resolution phantom and in ten healthy  
47 subjects with isotropic resolution of  $1.2\text{mm}^3$  and  $0.9\text{mm}^3$  and undersampling factors of x5  
48 and x9. 3D-PROST was compared against fully-sampled ( $1.2\text{mm}^3$  only), conventional  
49 parallel imaging and compressed sensing reconstructions.

50 **Results:** Phantom and in vivo ( $1.2\text{mm}^3$ ) reconstructions were in excellent agreement with  
51 the reference fully-sampled image. In vivo average acquisition times (min:sec) were  
52  $7:57 \pm 1:18$  (x5) and  $4:35 \pm 0:44$  (x9) for  $0.9\text{mm}^3$  resolution. Sub-millimeter 3D-PROST  
53 resulted in excellent depiction of the left and right coronary arteries including small  
54 branch vessels, leading to further improvements in vessel sharpness and visible vessel  
55 length in comparison with conventional reconstruction techniques. Image quality rated by  
56 two experts demonstrated that 3D-PROST provides good image quality and is robust even  
57 at high acceleration factors.

58 **Conclusion:** The proposed approach enables free-breathing whole-heart 3D CMRA with  
59 isotropic sub-millimeter resolution in less than 5 minutes and achieves improved coronary  
60 artery visualization in a short and predictable scan time.

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62 **Keywords:** coronary MR angiography; isotropic sub-millimeter resolution; respiratory  
63 motion; variable-density undersampling, patch reconstruction; accelerated imaging

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## 83 **Introduction**

84 Three-dimensional (3D) whole-heart coronary magnetic resonance angiography (CMRA)  
85 has shown significant potential for both diagnosis and characterization of coronary artery  
86 disease (CAD) without radiation exposure or the need for intravenous contrast (1–3).  
87 Previous studies have shown good diagnostic accuracy of conventional CMRA for the  
88 identification of significant CAD (defined as luminal stenosis  $> 50\%$ ) in the proximal-mid  
89 coronary segments compared to the non-invasive gold-standard computed tomography  
90 coronary angiography (4), demonstrating its effectiveness as a screening tool. However,  
91 the low spatial resolution of conventional CMRA and its anisotropy impedes the  
92 quantification of luminal stenosis and hinders visualization of distal segments.

93 To address this challenge, isotropic sub-millimeter 3D CMRA is required for more  
94 accurate assessment of lesion severity and effective risk stratification of patients.  
95 However, such imaging is not clinically feasible with conventional fully-sampled free-  
96 breathing diaphragmatic-navigated (dNAV) CMRA, used to minimize respiratory motion,  
97 due to excessively long and unpredictable scan times since only a fraction of the acquired  
98 data is accepted for reconstruction (referred to as scan efficiency) (5,6). Several  
99 approaches have been proposed to compensate for respiratory motion and achieve 100%  
100 respiratory scan efficiency. 1D self-navigation techniques (7–11) repeatedly acquire the  
101 k-space center to infer the translational superior-inferior respiratory induced motion of the  
102 heart. To reduce motion estimation errors due to contribution from static tissues (e.g.  
103 chest wall), 2D and 3D image-based navigators (iNAV) approaches have been recently  
104 proposed (12–15). These methods use low-resolution images to estimate and correct for  
105 2D or 3D respiratory motion of the heart. Most of these approaches enable  $\sim 100\%$  scan  
106 efficiency resulting in  $\sim 50\%$  reduced scan time. In spite of these developments, scan  
107 times for sub-millimeter resolution images remain lengthy (16). For example, at an  
108 average heart rate of 70 beats/min, a fully-sampled whole-heart 3D Cartesian CMRA scan  
109 at  $0.9 \text{ mm}^3$  isotropic resolution may take as long as one hour using dNAV (5-mm gating

110 window) and assuming 50% scan efficiency, which may be reduced to ~30 min using  
111 motion correction techniques with 100% scan efficiency.

112 Another approach to overcome the prohibitively long acquisition times in isotropic  
113 whole-heart CMRA is to use undersampling techniques, such as parallel imaging (PI)  
114 (17–19) and compressed sensing (CS) (20–22). Sparsity of MR images has been  
115 extensively exploited with CS, which states that a measured signal can be accurately  
116 recovered from few samples, under the assumption that the measured signals are  
117 randomly sampled, the signal is sparse in some basis and a non-linear reconstruction is  
118 used to enforce sparsity and data consistency (23). PI and CS have been combined to  
119 further reduce isotropic 3D whole-heart CMRA (20,24) scan times. Recently, patch-based  
120 image reconstructions exploiting local redundancies and low-rank matrix structures have  
121 been introduced for MR reconstruction to lead to sparser representations (24,25). By  
122 modeling the similarity of image patches through block-matching, low-rank  
123 representation and 3D filtering, 2D patch-based reconstructions used in concert with  
124 dNAV acquisitions have been shown to outperform conventional CS CMRA by  
125 recovering better image details and edges, as well as exhibiting improved overall image  
126 quality (24,26). However, these techniques have not been combined with respiratory  
127 motion correction and may suffer from residual aliasing artifacts for high acceleration  
128 factors, which may compromise the diagnostic value of the reconstructed coronary artery  
129 images.

130 In this study, we sought to achieve sub-millimeter isotropic 3D whole-heart Cartesian  
131 CMRA in a short and predictable scan time by combining 2D iNAV respiratory motion  
132 correction with variable density spiral-like sampling and a novel 3D patch-based  
133 undersampled reconstruction. The proposed 3D Patch-based RecOnSTruction (3D-  
134 PROST) further exploits the inherent redundancies of the complex 3D anatomy of the  
135 coronary arteries using an effective and efficient low-rank framework.

## 136 **Methods**

### 137 *Whole-Heart Image Navigated Undersampled 3D CMRA Sequence*

138 A prototype free-breathing 3D whole-heart, electrocardiogram (ECG)-triggered, balanced  
139 steady-state free precession (bSSFP) sequence with variable density Cartesian  
140 undersampling was implemented by extending a previously proposed spiral-like Cartesian  
141 acquisition (27) following a similar approach to Cheng et al. (28). The  $k_y$ - $k_z$  phase-  
142 encoding plane is sampled following approximate spiral interleaves on the Cartesian grid  
143 with variable density along each spiral arm. One spiral arm is acquired per cardiac cycle  
144 and is then rotated from one cardiac cycle to the next one. The  $k_y$ - $k_z$  plane is then  
145 segmented in two sets of concentric rings, the first defining the fully-sampled k-space  
146 center and the second representing the accelerated spiral branches. The phase-encoding  
147 lines within each ring are sorted according to a defined increment angle from  $0^\circ$  to  $360^\circ$   
148 as in (27). The sampling of the branches is accelerated exponentially from the k-space  
149 center to its periphery. The size of the fully-sampled k-space center was optimized  
150 experimentally on several datasets (not reported here) and was set to 20% the size of  $k_y$   
151 and  $k_z$  encoding directions. This undersampled trajectory ensures a pseudo-random  
152 pattern through the cardiac cycle, resulting in incoherent aliasing which spreads  
153 irregularly in a noise-like fashion.

154 The acquisition of each spiral arm was preceded by a 2D iNAV to enable beat-to-beat 2D  
155 translational respiratory motion estimation/compensation (SI: superior-inferior, RL: right-  
156 left) and 100% scan efficiency. iNAVs were obtained by spatially encoding 14 startup  
157 echoes of the bSSFP CMRA sequence (29). 2D translational motion was estimated using  
158 a template-matching algorithm (30), with the template manually selected around the heart  
159 during acquisition planning. Motion compensation was performed by modulating the k-  
160 space data with a linear phase shift (31,32) to a reference position at end-expiration.  
161 Motion estimation/compensation was performed before 3D-PROST reconstruction and  
162 was implemented inline in the scanner software (Siemens Syngo MR, E11A, Siemens  
163 Healthcare, Erlangen, Germany). The proposed acquisition framework is depicted in the  
164 sequence diagram of Fig. 1a.

165 ***3D Patch-based low-rank RecOnSTruction (3D-PROST)***

166 The general formulation of sparse representation in terms of a redundant dictionary  
 167 considers a 3D image  $m$  as the approximation  $m \approx D\alpha$ , where  $D$  is a fixed dictionary and  
 168  $\alpha$  a sparse vector satisfying the sparsity-inducing condition  $\|\alpha\|_0 \leq T$ , where the  $l_0$ -norm  
 169 counts the number of nonzero elements in  $\alpha$  and  $T$  is a predefined threshold. Strictly  
 170 speaking, the image  $m$  can be represented with a minimum number of sparse coefficients  
 171  $\alpha$  in the redundant dictionary  $D$ . In this study, we propose a novel reconstruction  
 172 algorithm which iteratively exploits the structure redundancy in the acquired data  $m$  to  
 173 construct a specific dictionary  $D$  for each group of similar 3D patches.

174 The proposed 3D-PROST scheme for isotropic CMRA reconstruction using 3D patch  
 175 redundancy is formulated as the following unconstrained optimization on the sparse  
 176 coefficients  $\alpha$  (33):

$$\operatorname{argmin}_{\alpha} \frac{1}{2} \|AFS_c D\alpha - K\|_2^2 + \lambda \|\alpha\|_0 \quad [1]$$

177 Where  $S_c$  are the known coil sensitivities for channel  $c$ ,  $F$  is the Fourier transform,  $A$  is  
 178 the sampling operator,  $K$  is the acquired multi-channel k-space data, and  $\lambda$  is the  
 179 regularization parameter. By introducing a variable  $m$  and considering the acquisition  
 180 model  $E = AFS_c$ , we transform Eq. [1] into its equivalent constrained minimization  
 181 problem

$$\operatorname{argmin}_{m, \alpha} \frac{1}{2} \|Em - K\|_2^2 + \lambda \|\alpha\|_0 \quad s.t. \quad m = D\alpha \quad [2]$$

182 Where  $m$  denotes the image to recover. One strategy to solve this minimization problem  
 183 is to approximate Eq. [2] using its augmented Lagrangian formulation (34), which implies  
 184 minimizing the augmented Lagrangian  $\mathcal{L}$ , defined below, with regards to  $m$ ,  $\alpha$  and  $b$

$$\mathcal{L}_{3DPROST}(m, \alpha, b) = \frac{1}{2} \|Em - K\|_2^2 + \lambda \|\alpha\|_0 + \frac{\mu}{2} \|m - D\alpha - b\|_2^2 \quad [3]$$

185 where  $b$  represents the Lagrange multiplier associated with the constraint “ $m = D\alpha$ ”, and  
 186  $\mu \geq 0$  is the penalty parameter. We solve Eq. [3] using a variable splitting approach by

187 alternating the minimization with respect to the image  $m$  (Optimization 1) and the sparse  
 188 coefficients  $\alpha$  (Optimization 2), followed by an update of the augmented multiplier  $b$ , and  
 189 repeating these three steps until a convergence criterion is satisfied. The rationale behind  
 190 this splitting approach is that each sub-problem is now much simpler to solve than the  
 191 original unconstrained problem in Eq. [1].

192 *Optimization 1: MR Reconstruction Update*

193 The first sub-problem with regards to the variable  $m$  is a conventional MR reconstruction  
 194 that incorporates the denoised volume  $D\alpha$  (obtained at the end of stage 2) as prior  
 195 information, using  $l_2$ -norm regularization:

$$\mathcal{L}_{MR\text{recon}}(m): \operatorname{argmin}_m \frac{1}{2} \|Em - K\|_2^2 + \frac{\mu}{2} \|m - D\alpha - b\|_2^2 \quad [4]$$

196 Differentiating with respect to  $m$ , the residual gradient step is defined by:

$$r = E^H Em - E^H K + \mu(m - \omega - b) \quad [5]$$

197 Where the operator  $E^H$  denotes the Hermitian transpose of  $E$  and  $\omega = D\alpha$  represents the  
 198 truncated singular value decomposition (SVD) reconstruction obtained at stage 2. For the  
 199 initialization,  $\omega$  and  $b$  were set to 0, which reduce the reconstruction problem to a  
 200 standard iterative SENSE with Tikhonov regularization. We use the gradient descent  
 201 optimization method to iteratively update the reconstructed volume  $m$ :

$$m^{(t+1)} \leftarrow m^{(t)} - \beta r^{(t)} \quad [6]$$

202 Where the relaxation parameter  $\beta$  can be updated iteratively or be set to a specific value  
 203 (e.g.  $\beta = 0.1$ ) to ensure convergence.

204 *Optimization 2: 3D Patch-Based Denoising Update*

205 The second sub-problem minimizes with respect to the sparse coefficients  $\alpha$  and is given  
 206 by

$$\mathcal{L}_{Patch}(\alpha): \operatorname{argmin}_{\alpha} \frac{1}{2} \|m - D\alpha - b\|_2^2 + \lambda \|\alpha\|_0 \quad [7]$$

207 Considering that sparse image coding is a local model representation and that neighboring  
 208 patches in CMRA images are highly redundant, this optimization can be performed on an  
 209 image patch basis approximating the  $l_0$ -norm by hard-thresholding. A 3D patch  $m_k$  in the  
 210 previously reconstructed volume  $m$  of size  $N$  voxels is defined as a small 3D block of  
 211 size  $n^3$  voxels around the voxel at index  $k$ . We define the operator  $R_k$  that extracts the  
 212 patch  $m_k$  from the image  $m$ :  $m_k = R_k(m)$ . Inversely, the image  $m$  can be recovered from  
 213 its set of patches using:

$$m = \left( \sum_{k=1}^N R_k^H(m_k) \right) ./ \left( \sum_{k=1}^N R_k^H R_k \right) = \left( \sum_{k=1}^N R_k^H(D_k \alpha_k) \right) ./ \left( \sum_{k=1}^N R_k^H R_k \right) \quad [8]$$

214 Where the operator  $R_k^H R_k$  is a matrix of same size as  $m_k$  with all elements being 1 (i.e.  
 215 averaging matrix) and the operator  $./$  denotes the element-wise division. Equation [7] can  
 216 thus be rewritten as the following patch-based minimization:

$$\operatorname{argmin}_{\alpha_k} \frac{1}{2} \|m_k - D_k \alpha_k - b_k\|_2^2 + \lambda \|\alpha_k\|_0 \quad \text{for } k = 1, \dots, N \quad [9]$$

217 The key of an efficient resolution of this optimization problem lies in the good choice of  
 218 the dictionary  $D_k$  which induces the highest sparsity in its associated group of similar  
 219 patches, and how accurately the sparse coefficients  $\alpha_k$  can be recovered from this  
 220 dictionary. In 3D patch-based representation, we consider the self-similarity as a 4D set of  
 221 similar 3D patches  $[m_1, \dots, m_L]$ , and its associated sparse coefficients  $[\alpha_1, \dots, \alpha_L]$  obtained  
 222 from a specific dictionary. In previous studies, transform-domain based on 3D fast  
 223 Fourier transform were successfully used to promote sparsity in the self-similarity group  
 224 built from 2D patches, followed by hard-thresholding and Wiener filtering to reduce the  
 225 apparent blurring artifacts (24). In order to account for 3D patches, here we reduce the  
 226 complexity of the problem by concatenating each similar vectorized 3D patch into a 2D  
 227 matrix. This 2D matrix, containing a high degree of similarity, exhibits a low-rank

228 structure which can be sparsely approximated using SVD. The low-complexity self-  
 229 adaptive dictionaries  $D_k$  are thus designed using SVD to sparsely represent each group of  
 230 similar patches, where the sparse coefficients  $[\alpha_1, \dots, \alpha_L]$  are represented, for each group,  
 231 by a few dominant singular values. Using the unitary property of the SVD, the  
 232 minimization problem in Eq. [9] is equivalent to minimizing with regards to the sparse  
 233 coefficients the following equation (33)

$$\mathcal{L}_{Patch}^k(\alpha): \underset{\alpha_k}{\operatorname{argmin}} \frac{1}{2} \|\tilde{\alpha}_k - \alpha_k\|_2^2 + \lambda \|\alpha_k\|_0 \quad [10]$$

234 Where  $\tilde{\alpha}_k$  are the sparse coefficients associated with  $m_k - b_k = \tilde{m}_k$  and  $\lambda > 0$  controls  
 235 the strength of sparsity. The lower the parameter  $\lambda$ , the more accurate the reconstructed  
 236 solution, at the price of reducing the sparseness. The solution of Eq. [10] can be obtained  
 237 using hard-thresholding (35)

$$\alpha_k^* = H_{\sqrt{2\lambda}}(\tilde{\alpha}_k) \quad [11]$$

238 Where  $H_\theta(\cdot)$  is the element-wise hard-thresholding operator, defined for a scalar  $v$  as:  
 239  $H_\theta(v) = \theta \cdot 1_{|v| > \theta}$ . In other words, any singular value  $\tilde{\alpha}_k$  below  $\sqrt{2\lambda}$  is set to 0. Note that  
 240 only the singular values are modified, but the singular vectors are unperturbed. This step  
 241 is repeated for each voxel in the volume  $m$  and the final denoised 3D volume  $\omega = D\alpha$  is  
 242 obtained by aggregating the multiple estimates  $D_k \alpha_k^*$  at each voxel location  $k = 1, \dots, N$ .  
 243 The Lagrange multiplier is then updated at iteration  $t + 1$  as

$$b^{(t+1)} \leftarrow b^{(t)} + \tau(\omega^{(t+1)} - m^{(t+1)}) \quad [12]$$

244 Where the penalty parameter  $\tau$  was set to 0.1 in all the experiments.

245 Optimizations [4] and [10] are processed iteratively to improve the accuracy of the  
 246 reconstructed volume. A flowchart illustrating all steps is shown in Fig. 1b. The effect of  
 247 exploiting 3D redundancy, instead of focusing on 2D patches (2D-PROST), is shown in  
 248 Supporting Fig. S2, which is available online.

## 249 **Image Reconstruction Implementation**

250 Like most MR reconstruction algorithms, the performance of the 3D-PROST technique  
251 relies on several parameters that need to be carefully tuned to get the best reconstruction.  
252 The central parameters of interest are the size of patch  $n$ , size of neighborhood window  $d$ ,  
253 number of selected patches  $L$ , regularization parameters  $\lambda$  and  $\mu$ , as well as the number of  
254 outer iterations (i.e. MR reconstruction and 3D denoising steps). The size of patch  $n$   
255 controls the degree of structural information within each patch. On one hand, a large  
256 value of  $n$  would capture the most geometric information and leads to a higher level of  
257 denoising, while a small value would act as a local filter and would potentially reduce the  
258 denoising performance of the algorithm. The computational cost of the algorithm is  
259 highly dependent on this parameter as well. For all the experiments, we set the size of  
260 patches to be  $5 \times 5 \times 5$  voxels and the search window  $d$  to 14, which gives a good tradeoff  
261 between reconstruction quality and computation time. The number of selected similar  
262 patches  $L$  did not seem to affect the quality of the reconstructions, thus we empirically set  
263 the value of  $L$  to 40, to avoid high computation cost and excessive memory requirements  
264 associated with large values of  $L$ . The performance of 3D-PROST was evaluated by  
265 comparing reconstructions (not reported here) with several similarity thresholds  $\lambda$  and  
266 regularization parameter values  $\mu$ . The optimal value ranges were determined, and we  
267 empirically set the values  $\lambda = 0.1$  and  $\mu = 0.3$  in all experiments. Coil sensitivity maps  
268 were estimated from the fully-sampled k-space center using the adaptive coil combination  
269 technique (36) and four outer iterations were chosen for all experiments as a good tradeoff  
270 between computational speed and reconstruction quality.

271 3D-PROST reconstruction was performed offline on a workstation with a 16-core Dual  
272 Intel Xeon Processor (2.3 GHz, 256GB RAM) with the MR reconstruction step  
273 implemented in Matlab (v7.1, MathWorks, Natick, MA) and the 3D denoising step in C to  
274 reduce the computational time. The proposed 3D-PROST reconstruction was compared to  
275 iterative SENSE (itSENSE) (37) and a CS reconstruction with  $l_1$ -wavelet regularization,  
276 as implemented in the BART toolbox (38). The regularization parameter was carefully

277 tuned and set to  $\lambda_{CS} = 0.01$  in all studies. The CS and itSENSE algorithms were stopped  
278 after 30 and 5 iterations, respectively, since preliminary testing revealed that these  
279 numbers of iterations led to the best reconstructions.

280 The feasibility of the proposed framework was tested in phantom at isotropic resolution  
281  $0.9 \text{ mm}^3$  (see Supporting Fig. S1) and in vivo experiments at two different isotropic  
282 spatial resolutions:  $1.2 \text{ mm}^3$  and  $0.9 \text{ mm}^3$ . All experiments were performed on a 1.5T  
283 scanner (Siemens Magnetom Aera, Erlangen, Germany) using 18-channel body and 32-  
284 channel spine coils. Written consent was obtained from all participants before undergoing  
285 CMRA scans and the study was approved by the Institutional Review Board.

### 286 *In vivo Study*

287 Ten healthy subjects (five men and five women, mean age:  $31 \pm 8$  years, range: 25-52  
288 years) underwent ECG-triggered free-breathing whole-heart CMRA using the proposed  
289 acquisition approach. Relevant scan parameters included: 3D bSSFP sequence, coronal  
290 orientation, FOV =  $320 \times 320 \times 86\text{-}115 \text{ mm}^3$ , FA= $90^\circ$ , T2-preparation duration= $40 \text{ ms}$ ,  
291 subject dependent mid-diastolic trigger delay and acquisition window (range 90-130 ms).  
292 To ensure adequate fat suppression, a SPIR fat saturation pulse was applied prior to  
293 imaging with a constant flip angle of  $130^\circ$ . A 2D iNAV preceded each spiral acquisition  
294 to achieve 100% scan efficiency and predictable scan time. 3D CMRA acquisitions were  
295 performed in the coronal plane.

### 296 *Impact of Undersampling on Reconstruction*

297 The proposed 3D-PROST reconstruction was evaluated for undersampling factors of x5  
298 and x9 in acquisitions with isotropic  $1.2 \text{ mm}^3$  resolution in comparison to a fully-sampled  
299 reference scan, which can be performed within a reasonable acquisition time at this  
300 resolution. Specific acquisition parameters for this study included: TE= $1.5 \text{ ms}$ , TR= $3.4 \text{ ms}$ ,  
301 bandwidth per pixel  $875 \text{ Hz}$ .

302 Acquired translational motion-corrected data was reconstructed with itSENSE, CS and  
303 the proposed 3D-PROST. Reconstructed images were reformatted along the right (RCA)

304 and left anterior descendent (LAD) coronary arteries and visible vessel length and vessel  
305 sharpness (first 4 cm and full length) were measured using Soap-Bubble (39).

306 Two experienced cardiologists (T.F.I and I.R, 9 and 3 years of experience respectively,  
307 SCMR level III certification), who were blinded to the reconstruction techniques,  
308 evaluated the quality of the reconstructed images. For each undersampling factor and each  
309 subject, the experts viewed the reformatted images (fully-sampled, itSENSE, CS, and 3D-  
310 PROST) in a random order and ranked the quality of both RCA and LAD from worst  
311 (score 1) to best (score 4). In addition, reconstruction quality based on RCA and LAD  
312 delineations was assessed using a 4-point scoring system with 1 indicating uninterpretable  
313 CMRA images; 2 indicating poor image quality (blurred edges, noise and residual  
314 artifacts, low confidence in the diagnosis); 3 indicating acceptable image quality  
315 (RCA/LAD adequately visualized, only mildly blurred edges); and 4 indicating fully  
316 diagnostic images (excellent image quality with sharply defined coronary borders).

317 Vessel sharpness and length were assessed separately for the RCA and LAD using a two-  
318 tailed Student t-test. Statistical significance of the expert quality scores was evaluated  
319 using a Wilcoxon signed rank test.  $P$  values of 0.016 or less were considered to be  
320 statistically significant after Bonferroni correction for multiple comparisons. The fully-  
321 sampled CMRA acquisition served as the reference image for both the qualitative and  
322 quantitative analyses.

### 323 *Impact of Resolution on Coronary Visualization*

324 A second set of in vivo experiments was carried out to investigate the performance of the  
325 proposed approach for sub-millimeter isotropic 3D CMRA acquisition. For this, the ten  
326 healthy subjects were also scanned at a  $0.9 \text{ mm}^3$  isotropic resolution with undersampling  
327 factors of 5 and 9 using the proposed approach. The fully-sampled acquisition was  
328 prohibitively long for this resolution ( $\sim 40$  min). Imaging parameters for this study were  
329 set to the same values as for the previous in vivo experiment except for TE/TR=1.6/3.7ms  
330 and bandwidth per pixel=890Hz. The impact of resolution on coronary artery  
331 visualization was assessed by comparing the images acquired with  $0.9 \text{ mm}^3$  isotropic

332 resolution with the fully-sampled 1.2 mm<sup>3</sup> isotropic resolution acquisition and its  
333 corresponding 5-fold and 9-fold undersampled reconstructions.

334 For each 3D-PROST reconstructed image and both undersampling factors, visualization  
335 of proximal, middle and distal segments of the RCA and LAD were identified and scored  
336 on a 3-point scoring system for coronary visualization by the two experienced  
337 cardiologists. The coronary artery segments were graded as follows: 0: not visible; 1:  
338 partial visibility; 2: excellent visualization of the coronary artery segment. To test for  
339 statistical differences, a Wilcoxon signed rank test was used. The visible vessel length  
340 was also measured for both the RCA and LAD and tested for statistical differences with a  
341 two-tailed Student t-test. Statistically significant differences were defined as  $P < 0.025$   
342 after Bonferroni correction for multiple comparisons.

## 343 **Results**

344 Free-breathing whole-heart CMRA acquisitions and reconstructions were completed  
345 successfully in all subjects. The mean heart rate was  $60 \pm 12$  bpm (range, 44-90 bpm). The  
346 average denoising time for 0.9 mm<sup>3</sup> isotropic resolution (Optimization 2 of PROST) was  
347 about 25 seconds, while the average MR reconstruction time (Optimization 1 of PROST)  
348 was approximately 1 minute, resulting in a total average reconstruction time of about  
349 5min40sec for the whole 3D-PROST reconstruction using four outer iterations.

### 350 *Impact of Undersampling on Reconstruction*

351 The average imaging time (min:sec) for the fully-sampled 3D CMRA acquisition with  
352 isotropic resolution 1.2 mm<sup>3</sup> was  $22:30 \pm 4:54$  with 100% scan efficiency, which was  
353 significantly reduced with 5-fold undersampling ( $4:11 \pm 1:03$ ,  $P < 0.05$ ) and 9-fold  
354 undersampling ( $2:36 \pm 0:24$ ,  $P < 0.05$ ).

355 Reformatted RCA images from three representative subjects are shown in Fig. 2 for  
356 itSENSE, CS and 3D-PROST reconstructions in comparison to the reference fully-  
357 sampled image. For both undersampling factors, CS and 3D-PROST reduce blurring and  
358 suppress noise artifacts compared to itSENSE. 3D-PROST further improved the

359 delineation of the proximal segment of the RCA, achieving similar image quality to the  
360 fully-sampled reference.

361 Vessel sharpness (first 4 cm and full length) of the LAD and RCA are summarized in Fig.  
362 3. Coronary vessel sharpness obtained using 3D-PROST was higher compared with  
363 itSENSE and CS and as good, if not higher than the fully-sampled reference for both the  
364 5-fold and 9-fold undersampled scans (Fig. 3(a-b)), in spite of a considerable reduction of  
365 the total scan times. The impact of 3D-PROST on coronary vessel sharpness was  
366 particularly noted for high acceleration (x9) with sharpness in close agreement with the  
367 fully-sampled reference, while itSENSE and CS failed to preserve the anatomical edges  
368 of the coronaries. The visual quality scores (Fig. 3c) indicate that 3D-PROST and fully-  
369 sampled reconstructions have the best image quality, notably better than CS and itSENSE.  
370 Image rank of the RCA and LAD (Fig. 3d) yielded similar values between 3D-PROST  
371 and fully-sampled reconstructions, differentiating them from CS and itSENSE for both  
372 accelerations.

### 373 *Impact of Resolution on Coronary Visualization*

374 The average imaging time (min:sec) for the  $0.9 \text{ mm}^3$  sub-millimeter isotropic resolution  
375 3D CMRA data was  $7:57 \pm 1:18$  with 5-fold undersampling and  $4:35 \pm 0:44$  with 9-fold  
376 undersampling with 100% scan efficiency.

377 Representative CMRA reformats from five healthy subjects are shown in Fig. 4 for fully-  
378 sampled  $1.2 \text{ mm}^3$  resolution, x5 undersampled  $1.2 \text{ mm}^3$  resolution and x5 undersampled  
379  $0.9 \text{ mm}^3$  resolution. The 5-fold undersampled sub-millimeter 3D-PROST CMRA images  
380 provided the best image quality with clear delineation of the left coronary system and  
381 improved visualization of the distal segments. Note the presence of residual motion  
382 artifacts in the fully-sampled experiments, particularly in subject 4, which may be  
383 associated with the long scan times. Vessel sharpness improvement at sub-millimeter  
384 resolution is also observed. The distal portion of the LAD is better visualized with  $0.9$   
385  $\text{mm}^3$  isotropic resolution than with  $1.2 \text{ mm}^3$  isotropic resolution for both fully-sampled  
386 and 5-fold undersampled acquisitions, particularly in subjects 4 and 6. In subject 8, the

387 sub-millimeter resolution provides the best delineation of the first diagonal branch and its  
388 bifurcation of the LAD, while this segment appears blurred and hardly distinguishable in  
389 the lower resolution images.

390 The quantitative and qualitative evaluations for the fully-sampled  $1.2 \text{ mm}^3$ , x5  
391 undersampled  $1.2 \text{ mm}^3$  and x5 undersampled  $0.9 \text{ mm}^3$  reconstructed images are provided  
392 in Fig. 5. The visible lengths were higher with  $0.9 \text{ mm}^3$  isotropic resolution with both 5-  
393 fold undersampling and 9-fold undersampling than the fully-sampled reference acquired  
394 at an isotropic resolution of  $1.2 \text{ mm}^3$ , while the scan time was significantly shorter (5-  
395 fold:  $7:57 \pm 1:18$ , 9-fold:  $4:35 \pm 0:44$  vs. fully-sampled  $22:30 \pm 4:54$ ). Vessel lengths  
396 obtained with 3D-PROST at sub-millimeter isotropic resolution and undersampling factor  
397 of 9 were higher than the lower-resolution  $1.2 \text{ mm}^3$  isotropic resolution undersampled by  
398 a factor of 5 (Fig. 5a), while the total scan times were similar ( $4:11 \pm 1:3$  vs.  $4:35 \pm 0:44$ ).  
399 Coronary visualization of the proximal and middle segments of the RCA and LAD  
400 yielded similar values between the  $1.2 \text{ mm}^3$  and  $0.9 \text{ mm}^3$  isotropic acquisitions. However,  
401 the distal segments were better visualized with  $0.9 \text{ mm}^3$  isotropic resolution, even for  
402 highly accelerated acquisitions (Fig. 5b-c).

403 Reformatted coronary artery images of two representative subjects acquired with sub-  
404 millimeter resolution and 100% scan efficiency are shown in Fig. 6 for zero-filling (ZF),  
405 itSENSE, CS and 3D-PROST reconstructions. Visualization of the left coronary system  
406 was improved with itSENSE relative to the ZF reconstruction. Reconstruction with CS  
407 improved the visualization of the distal segments while reducing noise and preserving the  
408 underlying coronary structures. 3D-PROST reconstruction led to substantial improvement  
409 in vessel sharpness and overall image quality. The accelerated sub-millimeter images  
410 combined with 3D-PROST reconstruction enable to capture the entire coronary tree and  
411 the surrounding vessels with high quality. Thin structures, such as the conus artery  
412 branching from the proximal RCA on subject 7 are intrinsically preserved, despite high  
413 acceleration factors (see Supporting Video S1).

## 414 **Discussion**

415 In this study, we proposed a framework for highly-accelerated sub-millimeter free-  
416 breathing 3D CMRA that combines 2D translational respiratory motion correction, with a  
417 variable density spiral-like Cartesian trajectory and a novel 3D-PROST reconstruction.  
418 The proposed approach enables sub-millimeter CMRA acquisitions in a fast and  
419 predictable scan time. The use of iNAV enables a substantial reduction of scan time  
420 compared to conventional dNAV scan, as has been previously shown (31,40), while the  
421 use of the proposed acquisition trajectory and reconstruction enables further acceleration.

422 The performance and feasibility of the proposed framework were assessed on a phantom  
423 and in ten healthy subjects. Phantom acquisitions were performed to evaluate the impact  
424 of undersampling on the reconstructed resolution. The undersampled variable density  
425 spiral-like Cartesian sampling introduces incoherent noise-like artifacts, which lead to  
426 robust patch matching during 3D-PROST reconstruction and thus high image quality  
427 reconstruction. At high undersampling, the fine structures of the resolution phantom were  
428 hardly detectable with zero-filled reconstruction, but the use of similarity through 3D  
429 patch matching and low-rank thresholding within 3D-PROST led to successful 3D  
430 reconstructions with preservation of resolution as demonstrated by the measured MTF  
431 (see Supporting Fig. S1).

432 The proposed 3D-PROST reconstruction integrates self-similarity information, by  
433 grouping 3D patches with similar structures. Low-rank properties and sparsity of the  
434 group are enforced to reduce the noise of the reconstructed volume while the MR  
435 reconstruction step was used to recover an isotropic 3D volume and enforce data fidelity.  
436 An augmented Lagrangian formulation was used to efficiently decompose the main cost  
437 function into two sub-problems that have straightforward solutions. The improved  
438 performance can be explained by the fact that CMRA images contain a rich amount of  
439 correlated 3D structures and therefore high sparsity degree can be achieved by merging  
440 this information. The increased sparsity of the proposed framework promotes superior  
441 denoising and structures recovery in comparison to other established approaches such as  
442 itSENSE or CS. Similar image quality was achieved with the proposed framework in  
443 comparison to the reference fully-sampled acquisition for an isotropic  $1.2 \text{ mm}^3$  resolution.

444 The significant scan time reduction achieved with the proposed framework was exploited  
445 to enable sub-millimeter ( $0.9 \text{ mm}^3$ ) whole-heart Cartesian CMRA in clinically feasible  
446 scan times. While comparable visualization of the proximal and middle segments was  
447 observed between  $1.2 \text{ mm}^3$  and  $0.9 \text{ mm}^3$  isotropic resolutions, visualization of the distal  
448 coronary segments was further improved at  $0.9 \text{ mm}^3$  isotropic resolution, even for highly  
449 accelerated acquisitions. In some cases, the proposed approach outperformed the image  
450 quality of the fully-sampled  $1.2 \text{ mm}^3$  acquisition in terms of sharpness. This may be partly  
451 explained by the significantly longer scan times of the fully-sampled acquisitions which  
452 are more prone to motion artifacts due to considerable drift in breathing pattern during  
453 imaging as well as non-rigid cardiac deformations that propagate over the acquisition  
454 (41,42). Conversely, the proposed approach enables the acquisition of 3D CMRA data in  
455 a relatively short time period, thus reducing the susceptibility to cardiac motion and  
456 respiratory drift.

457 A limitation of the present study is that, while 2D image-based navigation enables 100%  
458 scan efficiency and drastically reduces the scan time, this technique only enables 2D  
459 translational respiratory motion correction. This issue was however not shown to be  
460 significant in the present work when acquiring sub-millimeter resolution dataset in  
461 healthy subjects. This limitation can be overcome by incorporating non-rigid motion  
462 correction of respiratory motion in the reconstruction problem, as reported in previous  
463 studies (31,40,43). The design of 3D-PROST as a separate 3D patch-based optimization  
464 and a MR reconstruction problem enables the straightforward integration of non-rigid  
465 motion in the acquisition operator  $E$ , without affecting the 3D patch-based denoising step.  
466 This formulation would greatly benefit from an increase in image quality, particularly in  
467 patients with irregular breathing patterns, at the expense of increased reconstruction  
468 times. The impact of integrating non-rigid motion-correction into accelerated sub-  
469 millimeter isotropic CMRA acquisitions has not yet been established and is currently  
470 under investigation. Furthermore, arrhythmia detection/rejection approaches (44,45) can  
471 be included to further improve image quality and prevent residual cardiac motion artefacts  
472 due to irregular R-R intervals. Additionally, 3D image-based navigators can be

473 implemented and used to estimate beat-to-beat 3D translational displacements and to  
474 correct k-space data for respiratory motion (13,14), however they may lead to longer  
475 delays between preparation pulses and the 3D CMRA acquisition.

476 The proposed reconstruction method iterates between self-similarity extraction, rank  
477 reduction and MR reconstruction. Although motion correction was performed in-line with  
478 the scanner software, integration of the proposed 3D-PROST technique for in-line  
479 reconstruction is currently under development. Reconstruction times were in the order of  
480 5min for each dataset. The formulation of the 3D-patch extraction and thresholding as  
481 reported in this paper strongly enables the use of graphic processing unit or clusters,  
482 which should thus offer the advantage of sub-minute 3D reconstructions. Future work will  
483 investigate these implementations to facilitate clinical translation.

484 Our technique could have direct clinical implications as it offers several potential  
485 advantages: i) high image quality and high-resolution CMRA reconstruction by exploiting  
486 the inherent 3D redundancy of the coronary anatomy structure, ii) high acceleration can  
487 be achieved leading to short scan times, improved patient comfort and reduction of  
488 respiratory motion artifacts, iii) fast and efficient implementation leading to clinically  
489 feasible reconstruction times. Although the results reported here are encouraging, further  
490 studies in larger patient cohorts are needed. Substantial clinical evaluations will help to  
491 verify the efficiency of the proposed framework. We also anticipate that this technique  
492 will enable the acceleration of other recently developed CMRA sequences. For example,  
493 techniques that simultaneously provide bright-blood and black-blood whole-heart data  
494 (46) or black-blood LGE and bright-blood CMRA (47) can be markedly accelerated and  
495 could be integrated into clinical routine using the present framework.

496 The performance of the proposed framework suggests an opportunity to reach even higher  
497 resolutions in the future, which will be crucial to accurately detect and characterize  
498 luminal stenoses in patients with coronary artery disease. For example, at  $0.7 \text{ mm}^3$   
499 isotropic resolution, a 9-fold accelerated 3D CMRA scan using the proposed framework

500 should take approximately 9mins (correspondingly, ~1.3h for a fully-sampled acquisition  
501 with 100% scan efficiency). Future work will investigate this extension.

## 502 **Conclusion**

503 We demonstrate the feasibility of combining an efficient variable density Cartesian  
504 sampling trajectory with 2D iNAV-based translational motion correction and 3D-PROST  
505 undersampled reconstruction to obtain isotropic sub-millimeter 3D coronary images under  
506 free-breathing in ~5min predictable scan time, which is crucial for its integration in  
507 routine clinical examinations. Ultimately, this technique might be useful for rapid  
508 screening of the major coronary vessels in patients with suspected coronary artery  
509 disease. Further clinical validation is now warranted.

## 510 **Acknowledgement**

511 The authors acknowledge financial support from: (1) EPSRC EP/P001009/, EPSRC  
512 EP/P007619, FONDECYT 1161051, FONDECYT 1161055, (2) Wellcome EPSRC  
513 Centre for Medical Engineering (NS/ A000049/1), (3) the Department of Health via the  
514 National Institute for Health Research (NIHR) comprehensive Biomedical Research  
515 Centre award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's  
516 College London and King's College Hospital NHS Foundation Trust. The views  
517 expressed are those of the authors and not necessarily those of the NHS, the NIHR or the  
518 Department of Health.

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## 680 Captions

681 **Figure 1:** Acquisition and motion correction (A) is performed with an undersampled 3D  
682 variable density spiral-like Cartesian trajectory (VD-CASPR), preceded by 2D image  
683 navigators (iNAV), T2 preparation and fat saturation pulses. iNAVs are used to estimate  
684 and correct for the beat-to-beat 2D translational respiratory-induced motion of the heart  
685 (Moco). 3D-PROST Reconstruction (B): 3D-PROST reconstruction involves 2 stages of  
686 an augmented Lagrangian optimization scheme. In stage 1, image reconstruction is  
687 performed with patch prior and data consistency enforcement. In stage 2, image denoising  
688 is performed using 3D block-matching, which groups similar 3D patches in the image,  
689 followed by a low-rank approximation of each group using SVD shrinkage. The denoised  
690 volume from stage 2 is used in the reconstruction process in stage 1 as prior knowledge to  
691 regularize the reconstruction problem and further reduce noise.

692 **Figure 2:** Example reformatted images of the RCA from three representative healthy  
693 subjects acquired at  $1.2 \text{ mm}^3$  isotropic resolution with a fully-sampled whole-heart  
694 CMRA acquisition, and with two undersampled acquisitions (Acc x5 and Acc x9),  
695 reconstructed using iterative SENSE (itSENSE), wavelet-based compressed-sensing  
696 reconstruction (CS) and the proposed 3D patch-based approach (3D-PROST). All  
697 acquisitions were performed under free-breathing with 100% respiratory efficiency. 3D-  
698 PROST provides higher image quality and sharpness (red and yellow arrows) than  
699 itSENSE and CS for both acceleration factors, achieving similar image quality to the  
700 fully-sampled reference. Acquisition times (AT) are expressed as min:sec.

701 **Figure 3:** Quantitative coronary vessel sharpness for the first 4 cm (A) and the full length  
702 (B) and qualitative visual score (C) and image ranking (D) results from ten healthy  
703 subjects who underwent 100% scan efficiency accelerated CMRA with isotropic  
704 resolution  $1.2 \text{ mm}^3$  and two different undersampling factors (x5 and x9). A vessel  
705 sharpness of 100% marks an abrupt change in signal intensity whereas a sharpness of 0%  
706 indicates the absence of an edge. Results are expressed as mean  $\pm$  standard deviation.  
707 Differences with statistical significance are identified by \* $P < 0.016$  (ns = not significant).

708 **Figure 4:** CMRA images of five representative healthy subjects reformatted along the  
709 LAD and RCA with fully-sampled and 5-fold undersampled  $1.2 \text{ mm}^3$  isotropic resolution  
710 and 5-fold undersampled  $0.9 \text{ mm}^3$  isotropic resolution using the proposed acquisition and  
711 3D-PROST reconstruction approach. Close-up views are shown for each reconstruction.  
712 Acquisition times (AT) are expressed as min:sec.

713 **Figure 5:** Quantitative coronary vessel length (A) and qualitative visual score of the RCA  
714 (B) and LAD (C) from ten healthy subjects (N=10) who underwent accelerated CMRA  
715 with isotropic resolution  $1.2 \text{ mm}^3$  and  $0.9 \text{ mm}^3$  and with two different undersampling  
716 factors (5 and 9). Results are expressed as mean  $\pm$  standard deviation. Differences with  
717 statistical significance are identified by \*P < 0.025 (ns = not significant).

718 **Figure 6:** CMRA images reformatted along LAD for two representative healthy subjects.  
719 Acquisitions were performed with isotropic  $0.9 \text{ mm}^3$  resolution and 100% respiratory  
720 efficiency. Accelerated acquisitions with two different undersampling factors (x5 and x9)  
721 are shown. Motion-corrected images were reconstructed using zero-filling (ZF), iterative  
722 SENSE (itSENSE), a Wavelet-based compressed-sensing reconstruction (CS), and the  
723 proposed 3D patch-based technique (3D-PROST). 3D-PROST provides higher image  
724 quality than ZF, itSENSE and CS for both acceleration factors, with clear depiction of the  
725 left and right coronary systems as well as thin surrounding vessels (e.g. conus branching  
726 on Subject 7). Scan times are expressed as min:sec. AT = acquisition time, RCA = right  
727 coronary artery, LAD = left anterior descending artery, LM = left main, LCX = left  
728 circumflex, DIAG = diagonal branch.

729 **Supporting Figure S1:** Examples for the application of the proposed highly  
730 undersampled 3D-PROST approach on a high-resolution phantom. Fully-sampled  
731 acquisition (FS-left column) is compared to 5-fold and 9-fold accelerated acquisitions  
732 (middle and right columns respectively), for both zero-filled (ZF-top row) and 3D-  
733 PROST (middle row) reconstructions. The variable density undersampled Cartesian  
734 images with ZF reconstruction show significant blurring and contrast loss, while the 3D-  
735 PROST images exhibit sharp edges with faithful preservation of small details (as shown

736 on the cross-section profiles). Reconstructed resolution for ZF and the proposed 3D-  
737 PROST technique are shown on the top-left corner (modulation transfer function (MTF)  
738 profiles are taken in the pink box). Differences with statistical significance are identified  
739 by  $*P < 0.05$  (versus FS).

740  
741 **Supporting Video S1:** Example reconstructions from two healthy subjects with  
742 acceleration x9 (total acquisition times of 3:59 and 4:30 [min:sec]) and isotropic  
743 resolution 0.9 mm<sup>3</sup> are shown. Increasing image resolution to sub-millimeter isotropic  
744 voxels with the proposed variable density Cartesian sampling and 3D-PROST  
745 reconstruction allows reliable depiction of extensive portions of the right and left  
746 coronary systems.

747  
748 **Supporting Figure S2:** Coronal (a), sagittal (b) and transversal (c) views of CMRA  
749 images reconstructed using iterative SENSE (itSENSE), the proposed framework with  
750 2D-patches of size 5x5 voxels and a search window of 14x14 voxels (2D-PROST) and  
751 3D-patches of size 5x5x5 voxels with a search window of 14x14x14 voxels (3D-PROST).  
752 The 3D CMRA acquisition was performed in free-breathing in one healthy subject with  
753 an undersampling factor of 5 and 100% scan efficiency. Images reformatted along the left  
754 (LAD) and right (RCA) coronary arteries are shown on the right. 3D-PROST provides  
755 better image quality than 2D-PROST, reducing streaking artifacts (yellow arrows). RV =  
756 right ventricle, RCA = right coronary artery, LAD = left anterior descending artery, PA =  
757 pulmonary artery, SVD = superior vena cava, AO = aorta, LM = left main, LCX = left  
758 circumflex, PT = pulmonary trunk.

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