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1   **Importance of operator training and rest perfusion**

2   **on the diagnostic accuracy of stress perfusion cardiovascular magnetic**

3   **resonance**

4

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132   **Abstract**

133   **Background:** Clinical evaluation of stress perfusion cardiovascular magnetic

134   resonance (CMR) is currently based on visual assessment and has shown

135   high diagnostic accuracy in previous clinical trials, when performed by

136   expert readers or core laboratories. However, these results may not be

137   generalizable to clinical practice, particularly when less experienced readers

138   are concerned. Other factors, such as the level of training, the extent of

139   ischaemia, and image quality could affect the diagnostic accuracy. Moreover,

140   the role of rest images has not been clarified.

141   The aim of this study was to assess the diagnostic accuracy of visual

142   assessment for operators with different levels of training and the additional

143   value of rest perfusion imaging, and to compare visual assessment and

144   automated quantitative analysis in the assessment of coronary artery

145   disease (CAD).

146   **Methods:** We evaluated 53 patients with known or suspected CAD referred

147   for stress-perfusion CMR. Nine operators (equally divided in 3 levels of

148   competency) blindly reviewed each case twice with a 2-week interval, in a

149   randomised order, with and without rest images. Semi-automated Fermi

150   deconvolution was used for quantitative analysis and estimation of

151   myocardial perfusion reserve as the ratio of stress to rest perfusion

152   estimates.

153   **Results:** Level-3 operators correctly identified significant CAD in 83.6% of

154   the cases. This percentage dropped to 65.7% for Level-2 operators and to

155   55.7% for Level-1 operators (p<0.001). Quantitative analysis correctly

156   identified CAD in 86.3% of the cases and was non-inferior to expert readers

157 (p=0.56). When rest images were available, a significantly higher level of

158 confidence was reported (p=0.022), but no significant differences in

159 diagnostic accuracy were measured (p=0.34).

160 **Conclusions:** Our study demonstrates that the level of training is the main

161 determinant of the diagnostic accuracy in the identification of CAD. Level-3

162 operators performed at levels comparable with the results from clinical

163 trials. Rest images did not significantly improve diagnostic accuracy, but

164 contributed to higher confidence in the results. Automated quantitative

165 analysis performed similarly to level-3 operators. This is of increasing

166 relevance as recent technical advances in image reconstruction and analysis

167 techniques are likely to permit the clinical translation of robust and fully

168 automated quantitative analysis into routine clinical practice.

169

170 **<u>Keywords</u>**

171 Cardiovascular Magnetic Resonance, Stress Perfusion Imaging, Coronary

172 Artery Disease, Quantitative assessment, Myocardial Ischemia, Diagnostic

173 Accuracy, Training.

174

175 **<u>Abbreviation list</u>**

176 AHA: American Heart Association

177 CAD: coronary artery disease

178 CME: Continuous medical education

179 CMR: Cardiovascular magnetic resonance

180 EACVI: European Association of Cardiovascular Imaging

181 ESC: European Society of Cardiology

182   LAD: left anterior descending coronary artery

183   LCX: left circumflex coronary artery

184   LGE: late gadolinium enhancement

185   MBF: myocardial blood flow

186   MPR: myocardial perfusion reserve

187   RCA: right coronary artery

188   SCMR: Society for Cardiovascular Magnetic Resonance

189 **Background**

190 Stress perfusion cardiovascular magnetic resonance (CMR) is increasingly

191 used for the evaluation of patients with known or suspected coronary artery

192 disease (CAD) and has a class I indication for patients at intermediate risk of

193 CAD according to recent guidelines[1,2].

194 Stress perfusion CMR has been shown to be highly accurate for the detection

195 of CAD, with sensitivity ranging from 75% to 91% and specificity ranging

196 from 59% to 87%[3-5]. It should be noted that in most of these studies,

197 visual assessment has been carried out either by a core laboratory or by

198 expert readers, and therefore the findings may not be generalizable to

199 routine clinical practice. As stress perfusion CMR gains acceptance and

200 becomes more available, it will inevitably be performed in lower volume and

201 less experienced centers.

202 Stress perfusion CMR is typically evaluated by visual assessment. This can be

203 influenced by the extent of ischemia and the presence of areas of relatively

204 preserved perfusion, which can be used as reference[6]. Moreover, image

205 artefacts can complicate the interpretation of the images. Dark rim artefacts,

206 which are commonly observed during stress perfusion, can be misdiagnosed

207 as subendocardial perfusion abnormalities[7], in particular when relatively

208 long acquisition times are used and spatial resolution is low. Moreover,

209 areas of infarction are frequently associated with delayed perfusion[8,9].

210 The simultaneous evaluation of stress and rest perfusion CMR and late

211 gadolinium enhancement (LGE) images is recommended to identify areas of

212 myocardial infarction and improve the specificity of the

213 interpretation[10,11], and to exclude imaging artefacts[10].

214   Additionally, it has been suggested that rest perfusion images could play an

215   important role in improving the identification of imaging artefacts when

216   signal abnormalities are present on both stress and rest images[10]. The

217   acquisition of rest images enables quantification of perfusion reserve, but

218   prolongs scan times and requires additional contrast dosing.

219   Stress perfusion CMR is complex to read and requires significant training

220   and experience, however, the impact of training and experience has not been

221   formally studied and as yet, there are no specific recommendations in

222   current guidelines, apart from stating that stress perfusion CMR should be

223   part of the training program for Level-2 readers[12]. It is hoped that fully

224   quantitative automated methods may help bridge training gaps and support

225   clinical decision making.

226   We sought to determine the importance of the level of operator training of

227   the diagnostic accuracy of stress perfusion CMR; the role of rest perfusion

228   images in the identification of imaging artefacts and in the correct detection

229   of CAD; and to systematically compare the results of visual assessment with

230   semi-automated quantitative analysis to determine its additional value.

231

232   **Methods**

233   Consecutive patients (n=53) referred for stress perfusion CMR for suspected

234   CAD were retrospectively included in the study. All patients had invasive

235   coronary angiography on the basis of the clinical indication within 1 month

236   of the CMR examination. Exclusion criteria were contraindications to CMR,

237   gadolinium-based contrast agents or adenosine. Patients with previous

238   coronary artery bypass grafting, hypertrophic cardiomyopathy, aortic

239   stenosis, or other primary myopathic or valvular disease were excluded. All

240   subjects gave written informed consent in accordance with ethical approval.

241   This study complies with the Declaration of Helsinki.

242

243   **Image acquisition**

244   CMR images were acquired using a 3T scanner (Achieva, Philips Medical

245   Systems, Beth, The Netherlands) equipped with 32-channel phased-array

246   cardiac coil. The protocol included functional assessment, adenosine stress

247   and rest first pass perfusion imaging, and LGE. The images were acquired

248   using standard acquisition protocols and in end-expiratory breath-hold. For

249   stress imaging, 140 μg/kg/min of adenosine was administered. Imaging

250   commenced 3 min after infusion initiation. A dual bolus (equal volumes of

251   0.0075 mmol/kg followed by 0.075 mmol/kg after a 20-s pause) of contrast

252   agent (gadobutrol/Gadovist, Schering, Germany) was injected at 4 ml/s by a

253   power injector[13]. For perfusion, a saturation recovery prepared gradient

254   echo pulse sequence accelerated with k–t sensitivity encoding acceleration

255   with 11 training profiles was used. Typical imaging parameters were: 3

256   short-axis slices covering standard American Heart Association (AHA)

257   segments[14], 120 acquired dynamics/slice, flip angle 20°, TR 2.5 ms, TE

258   1.25 ms, saturation pre-pulse recovery time 100 ms, pixel size 1.9x1.9 mm,

259   slice thickness 10 mm.

260   Typical imaging parameters for LGE imaging were: long and short axis to

261   fully cover the left ventricle, inversion recovery turbo field echo, flip angle

262   25°, TR 6 ms, TE 3 ms, pixel size 0.7x0.7 mm, slice thickness 10 mm.

263

Operator selection

Nine operators were chosen amongst the physicians working in our unit and in other European institutions, on the basis of their level of competency, according to the European Society of Cardiology (ESC)/European Association of Cardiovascular Imaging (EACVI) training guidelines[12]. A total of 9 operators, 3 for each competency level, were chosen; all operators had recently obtained the ESC/EACVI certification (within 2 months) for the appropriate level. In brief, level-1 competency ESC certification requires 20 continuous medical education (CME) hours, involvement in 50 CMR cases and 1-month fellowship; level-2 requires at least 50 CME hours, involvement in 150 clinical cases of which 25 must be perfusion studies, a minimum of 3-months fellowship and the European CMR exam; level-3 requires at least 50 CME hours, involvement in 300 clinical cases of which a minimum of 50 must be perfusion studies, at least 12-months training and the European CMR exam. Level-1 competency reflects core CMR training, level-2 is required to report CMR studies with support from a Level-3 operator and Level-3 is required to perform, interpret and report CMR studies fully independently[12].

Image analysis – visual assessment

Each operator was asked to report each of the 53 scans twice over a 4-week period, with a minimum interval of 2 weeks between first and second read. The scans were anonymized and presented to the operator as a full dataset, including stress and rest perfusion and LGE, or as reduced datasets, including stress perfusion and LGE only. The full and reduced datasets were

289   analysed blinded to clinical and angiographic data and in a randomized

290   order on different days. The study flowchart can be seen in Figure 1.

291   Visual assessment of adenosine stress perfusion CMR and LGE images,

292   displayed side-by-side, was performed as per clinical practice, in accordance

293   with standardized CMR protocols[15]. A perfusion defect was defined as a

294   regional reduction in myocardial signal during LV first-pass of contrast

295   agent, not related to artefacts and not corresponding to an area of scar on

296   LGE images.

297   Operators were asked to fill an on-line standardized form and to identify

298   segments with inducible ischaemia, to identify the presence and

299   transmurality of LGE[16], to identify the most likely culprit coronary artery

300   based on the standard AHA segmentation[14], and to grade their confidence

301   in the diagnosis and the perceived image quality.

302   The confidence was graded as: 0- very unconfident, 1- unconfident, 2-

303   confident, 3- very confident. The perceived image quality was graded as: 0-

304   poor, 1- moderate, 2- good, 3- excellent.

305   Coronary angiography results have been used as reference standard. The

306   threshold for coronary artery lumen stenosis was 70% diameter stenosis for

307   epicardial vessels. All invasive angiographic images have been reviewed by

308   consensus of expert operators.

309

310   **Image analysis – quantitative assessment**

311   A different operator, blinded to results of visual perfusion assessment and

312   other clinical/angiographic data, performed the segmentation of the images

313   for semi-automated quantitative analysis using software and methods

314   previously developed and validated by our group. Respiratory motion was

315   corrected using affine image registration by maximization of the joint

316   correlation between consecutive dynamics within an automatically

317   determined region of interest[17]. A temporal maximum intensity projection

318   was calculated to serve as a feature image for automatic contour delineation

319   method. The operator then manually optimized the automatically generated

320   contours to avoid partial volume effects at the endocardial and epicardial

321   border[17]. The intervention of the operator was limited to image

322   segmentation. Quantitative perfusion analysis was then automatically

323   performed by Fermi-constrained deconvolution according to the methods

324   described by Wilke et al[18] and Jerosch-Herold et al[19], optimised for

325   high-resolution pixel-wise analysis [20,21]. Myocardial perfusion reserve

326   (MPR) was calculated as the ratio between stress and rest myocardial blood

327   flow (MBF) estimates. Ischaemia was defined as segments with MPR<1.5,

328   according to previously validated criteria[22,23].

329

330   **Statistical analysis**

331   Continuous variables are presented as mean±standard deviation for

332   normally distributed variables and as median with interquartile range for

333   non-parametric data. Normality was assessed with Q-Q plots and the

334   Kolmogorov-Smirnov test. Continuous variables were compared using an

335   unpaired Student *t test* or the Wilcoxon rank-sum test, as appropriate, and

336   categorical data were compared between groups using the Fisher exact test

337   and Pearson chi-square test. The McNemar test was used for paired

338   dichotomous data. Two-tailed values of p<0.05 were considered to be

339 statistically significant. One-way ANOVA was used to determine differences

340 between multiple groups. Bonferroni correction was used to account for

341 multiple testing.

342

343 **Results**

344 **Characteristics of the population**

345 The mean age of the population (n=53) was 60.6±12.7 years. Demographic

346 data are shown in Table 1. The prevalence of CAD in the group of patients

347 included in the analysis was 30.2%, with 16/53 patients positive for CAD on

348 invasive coronary angiography. Left anterior descending (LAD) lesions were

349 identified in 9 (17%) of the cases; left circumflex (LCX) lesions in 8 (15.1%)

350 of the cases; and right coronary artery (RCA) in 13 (24.5%) of the cases.

351 Within the group of patients with CAD, 8 patients had 1-vessel disease

352 (50%), 5 patients 2-vessel disease (31.3%) and 3 patients 3-vessel disease

353 (18.8%).

354

355 **Impact of operator training on correct CAD identification**

356 There was a significant correlation between an operator's training level and

357 the rate of correct identification of CAD on a per patient level on visual

358 assessment. The diagnosis of Level-3 operators agreed with invasive

359 coronary angiography in 83.6±2.3% of the cases, while this percentage

360 dropped to 65.7±4.3% for Level-2 operators and to 55.7±5.3% for Level-1

361 operators (p<0.001 between the 3 groups)(Figure 2). A significant difference

362 in the agreement with angiography between different levels of training was

363 also observed in a sub-analysis per coronary territory (p<0.001)(Figure 3).

364   When different perfusion territories were compared, the agreement

365   between CMR and coronary angiography was higher for the LAD territory,

366   followed by the LCX and by the RCA territories. The same trend was

367   observed in all groups of operators, regardless of the level of training

368   (p<0.001).

369   The sensitivity and specificity for operators of different levels of training are

370   reported in Figure 4. Level-1 operators showed high sensitivity (86.5±6.1%)

371   and low specificity (41.9±10.9%). Level-2 operators had a sensitivity of

372   57.3±4.7% and a specificity of 69.4±9.9%. Level-3 operators showed a

373   sensitivity of 71.9±13% and a specificity of 88.7±6.7% respectively. There

374   was a statistically significant difference for both sensitivity and specificity

375   between different levels of training (p<0.001)(Figure 4).

376

377   **Impact of rest perfusion on correct identification of CAD**

378   When rest images were available, there was no statistically significant

379   difference at all levels of training (Figure 5) and in the overall analysis

380   (69.6±14.3% vs 67.1±13.1%; p=0.34). However, when rest images were

381   available, a significantly higher level of confidence was reported by the

382   operators (*p*=0.022) and subjective image quality was scored at a higher

383   level (*p*=0.012).

384

385   **CAD classification**

386   Figure 6 shows a comparison between the extent of CAD identified by the

387   operators on CMR images in comparison with invasive coronary

388   angiography. An overestimation of the severity of CAD was observed in

17

389 Level-1 operators, regardless of the number of vessels with CAD. Despite

390 being more accurate, Level-2 and Level-3 operators significantly

391 underestimated the number of positive perfusion territories in patients with

392 multi-vessel CAD.

393

394 **Impact of quantitative analysis on correct CAD identification**

395 Quantitative analysis was successfully performed in 51 patients. In 2 cases of

396 patients without CAD, the automated algorithms failed and no results could

397 be calculated. In both cases, this was due to the low quality of the diluted

398 pre-bolus used for the estimation of the arterial input function. Level-3

399 visual assessment of the 2 cases where quantification failed yielded the

400 correct diagnosis in both cases when both stress and rest images were made

401 available to the readers, and in 66% of interpretations when only stress

402 perfusion was made available to the readers. Quantitative stress perfusion

403 CMR analysis agreed with the results of invasive angiography in 86.3% of the

404 cases, performing significantly better than Level-1 and Level-2 operators

405 (p<0.001). Level-3 visual assessment and quantitative analysis were not

406 significantly different (p=0.56)(Figure 2). Quantitative analysis had a

407 sensitivity of 68.8% and specificity of 94.3%. When the 2 cases in which

408 quantitative analysis failed are considered as a missed diagnosis, the

409 concordance of quantitative analysis with invasive angiography was 83%,

410 with a sensitivity of 68.8% and a specificity of 89.2%.

411

412 **Discussion**

413 This study has several important findings. Operator training and experience

414 had a significant impact on diagnostic accuracy. Only Level-3 trained

415 operators had an accuracy comparable with the results reported by large

416 clinical trials[3-5]. Rest images did not significantly improve the diagnostic

417 accuracy of stress perfusion CMR but, when available, contributed to a

418 significantly higher confidence of the operators in their reports and to a

419 higher perceived image quality, regardless of the level of training. Finally,

420 semi-automated quantitative analysis performed better than Level-1 and

421 Level-2 operators, but similarly to a Level-3 operator. Quantitative analysis

422 however failed in 2/53 cases due to technical reasons related to the

423 administration of a diluted pre-bolus. However, the same cases could be

424 analysed visually.

425 Stress perfusion CMR plays an increasingly important role in the evaluation

426 of patients with known or suspected CAD. Recent European guidelines

427 recommend the use of stress perfusion CMR in patients with suspected CAD

428 and intermediate pre-test probability, with a class 1 indication and level of

429 evidence A, similarly to stress echocardiography and nuclear imaging[1,2].

430 US guidelines recommend stress perfusion CMR with 2A indication[24],

431 particularly in specific subgroups of patients[25]. These indications are

432 based on the assumption that stress perfusion CMR is highly accurate for the

433 identification of CAD and compares favorably with other functional

434 modalities. In large trials and meta-analyses, the sensitivity ranged from

435 75%[3] to 91%[4] and specificity ranged from 59%[3] to 87%[5]. In the CE-

436 MARC study[26], sensitivity was 86.5% and specificity was 83.4%, and the

437 MR-IMPACT 2 trial[27] reported a sensitivity of 75% and a specificity of

438   59%. These wide intervals most likely represent the variability in study

439   design, the different prevalence of disease in different populations, and

440   variability in the criteria used for visual assessment.

441   The diagnostic accuracy of stress perfusion CMR reported in the literature is

442   often the result of visual assessment carried out by expert readers, which are

443   usually Level-3 operators and often are internationally recognized experts.

444   Our study demonstrates that the diagnostic accuracy varied significantly

445   amongst groups of readers with different levels of training, and reached

446   values comparable with those of large studies only in the group of Level-3

447   operators. These results confirm the high diagnostic accuracy of stress

448   perfusion CMR in comparison with coronary angiography, however clearly

449   indicate the need for Level-3 supervision when stress perfusion scans are

450   reported.

451   From the analysis of the sensitivity and specificity for the detection of CAD in

452   different groups, it emerges that Level-1 operators had high sensitivity

453   (86.5%). This came however at the cost of a reduced specificity (41.9%) and

454   rate of overall correct CAD detection (55.7%). Factors such as image quality

455   and the prevalence of dark rim artefacts, which can mimic the presence of

456   subendocardial perfusion defects, could have played a role. In comparison,

457   Level-3 operators under-called the disease (sensitivity 71.9%) but had a

458   high specificity (88.7%). All diagnostic investigations involve a trade-off

459   between sensitivity and specificity. At a population level and from a health-

460   economic perspective, we feel that the results achieved by Level 3 operators

461   represent a reasonable balance between the need to identify significant

462   coronary disease and the high specificity required to avoid increasing down-

463   stream investigation costs through increased referral for invasive coronary

464   angiography. The work of Patel et al[28] highlights the need for better

465   selection of patients for invasive investigation given the costs and potential

466   morbidity incurred by this.

467   Our results support the recommendations from the ESC [12], which state

468   that Level-1 operators hold the basic knowledge in CMR sufficient to select

469   appropriate CMR indications and interpret CMR reports, but are not cleared

470   to report CMR scans. This is reflected in our result by the fact that Level-1

471   operators demonstrated a very low diagnostic accuracy, with poor

472   specificity for the presence of CAD. According to the ESC guidelines, Level-2

473   operators may actively perform and report CMR, but are not completely

474   independent and should work under the supervision of a Level-3 expert.

475   This is also supported by our results, since Level-2 operators were

476   significantly less accurate than Level-3 operators. Level-3 operators instead

477   performed to levels similar to those reported by studies such as the CE-

478   MARC[26].

479   It should be noted that the Society for Cardiovascular Magnetic Resonance

480   (SCMR) guidelines on training[29] differ slightly from the ESC guidelines

481   used in this study to define the level of training of the operators. According

482   to the SCMR guidelines, Level-2 operators can independently report CMR

483   scans, whereas Level-3 certification has more to do with being able to lead a

484   CMR unit and perform research in the field. Both guidelines agree that Level-

485   1 training is not sufficient to practice CMR.

486

487   It has been suggested that rest perfusion images play an important role in

488   improving the identification of imaging artefacts when signal abnormalities

489   are present on both stress and rest images[10]. When assessing stress

490   perfusion CMR visually, guidelines advise displaying both rest and stress

491   images side-by-side to identify correctly inducible perfusion defect and

492   artefacts[10,11].

493   In our study, we did not find any significant difference in the diagnostic

494   accuracy when rest images were available. Our findings mirror those of

495   Biglands et al[30]. However, when testing the operator confidence and the

496   perceived image quality, a statistically significant difference was noted when

497   both stress and rest images were available. The increased confidence was

498   more evident for Level-1 and Level-2 operators.

499   Interestingly, Level-1 operators reported a higher confidence score than

500   more experienced operators, despite lower overall accuracy. This could

501   reflect a cognitive bias, also known as the Dunning-Kruger effect[31].

502   The diagnostic usefulness of rest perfusion imaging resides in the finding of

503   "fixed perfusion defect" on both stress and rest images, which may be

504   related to artefacts or to areas of myocardial infarction. However, this may

505   be overcome when stress perfusion CMR is assessed visually side-by-side

506   with LGE, as per guidelines[11] and as in our study. Nevertheless, rest

507   perfusion imaging remains a fundamental requirement for perfusion

508   quantification and MPR estimation.

509

510   Semi-automated quantitative assessment performed better than Level-1 and

511   Level-2 operators and similarly to Level-3 operators for the detection of

512 CAD. The latter is in keeping with the results of several other studies that

513 reported high sensitivity and specificity for quantitative analysis, with

514 sensitivity ranging from 80%[22] to 94.4%[32] and specificity ranging from

515 81%[33] to 100%[34]. Previous studies from Patel et al[6] and Mordini et

516 al[35] compared quantitative with visual and semi-quantitative analysis and

517 demonstrated that quantitative analysis is superior to visual assessment and

518 semi-quantitative assessment in the detection of ischemia, and that

519 quantitative analysis is the most accurate method to measure the total

520 ischemic burden.

521 In the present study, quantitative analysis was performed using a semi-

522 automated method which requires user input to confirm the automated

523 segmentation of the images but eliminates inter-observer variability for

524 what concerns the quantification procedure. This is of increasing relevance

525 as recent technical advances in image reconstruction and analysis

526 techniques are likely to permit the clinical translation of robust and fully

527 automated quantitative analysis into routine clinical practice [36-39]. In our

528 study however, the dual bolus approach used for arterial input function

529 measurements failed in 2 subjects, impeding quantitative analysis. The

530 advent of dual sequences capable of a more accurate assessment of the

531 concentration of gadolinium in the main bolus input function may make the

532 use of dual bolus redundant in the near future[37,40].

533

534 **Limitations**

535 This study included a selected population with suspected CAD and we

536 excluded patients with primary cardiomyopathy. Thus, our results on

537 diagnostic accuracy do not include other patterns of perfusion

538 abnormalities, which may require even more experience to discern (e.g.,

539 microvascular dysfunction).

540 Moreover, we used an anatomical reference standard (invasive coronary

541 angiography) to compare operators' performances in interpreting a

542 functional test, while a functional reference standard (e.g., fractional flow

543 reserve) may be more appropriate.

544 Our results demonstrate that similarly accurate detection of CAD can be

545 achieved by Level-3 operators and by automated perfusion quantification.

546 Although our study was not powered to demonstrate the superiority of

547 quantitative analysis, this has been the subject of a recent study which has

548 reported very similar findings[30]. The non-inferiority of automated

549 quantification to expert visual reads, in combination with the prognostic

550 value of quantitative analysis[23] will facilitate more widespread adoption

551 of stress perfusion CMR by less experienced readers.

552 Finally, all stress perfusion CMR were acquired in a single center, using a 3T

553 Philips scanner and a high-resolution k-t sequence. This may not reflect the

554 standard clinical acquisition in other centres.

555

556 **<u>Conclusions</u>**

557 This study demonstrates that visual assessment of stress perfusion CMR is

558 challenging for Level-1 and Level-2 operators but accurate in the hands of

559 Level-3 operators. Our results highlight the importance of the

560 recommendations of the ESC/EACVI training guidelines in CMR, which

561 recommend independent reporting for Level-3 operators only and

562   supervised reporting for Level-2 trained operators. The availability of rest

563   perfusion images was associated with significantly higher confidence and

564   higher perceived image quality, regardless of the level of training of the

565   operator. Quantitative analysis performed similarly to Level-3 trained

566   operators and could represent, in the future, a valid alternative to visual

567   assessment.

568

583

584   **Declarations**

585 **Ethics approval and consent to participate**: All subjects gave written

586 informed consent in accordance with ethical approval (ethics 15/NS/0030,

587 NHS Grampians Regional Ethics Committee).

588 **Consent for publication**: Not applicable.

589 **Availability of data and materials**: Please contact author for data requests.

590 **Competing interests**: The authors declare that they have no competing

591 interests.

592 **Funding**: This work was supported by the National Institute for Health

593 Research (NIHR) Cardiovascular Health Technology Cooperative (HTC) and

594 Biomedical Research Centre (BRC) awarded to Guy's & St Thomas' NHS

595 Foundation Trust in partnership with King's College London. This work was

596 additionally supported by the Wellcome/EPSRC Centre for Medical

597 Engineering at King's College London [WT 203148/Z/16/Z]. MSN was

598 funded through a fellowship from the Medical Research Council

599 [MR/P01979X/1]. All funding bodies equally contributed to the collection,

600 analysis, and interpretation of the data and to the investigators' salaries

601 during the study.

602 **Authors' contribution:** ADMV, LC, NB and AC conceived the study and

603 participated in the study design and coordination. IN, GDG, NC, CF, MSN, JK,

604 ES, VDF and AS analysed the data. ADMV, LC, XM, CS and TFI performed the

605 data analysis. AC segmented the data for quantitative analysis. ADMV and LC

606 drafted the manuscript. All authors critically revised the manuscript for

607 important intellectual content, read and approved the final manuscript.

608 **Authors' information**: Not applicable.

609 **Endnotes**: Not applicable.

610

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778

Figure titles and legends

780 **Figure 1**. Study flowchart.

781 CMR: cardiovascular magnetic resonance, LGE: late gadolinium

782 enhancement.

783

784 **Figure 2**. Percentage of correct coronary artery disease (CAD) identification

785 (diagnostic accuracy) for different levels of CMR training and using

786 quantitative assessment.

787 CAD: coronary artery disease, CMR: cardiovascular magnetic resonance.

788

789 **Figure 3**. Percentage of correct CAD identification (diagnostic accuracy)

790 stratified by coronary territory.

791 CAD: coronary artery disease, LAD: left anterior descending coronary artery,

792 LCX: left circumflex coronary artery, RCA: right coronary artery.

793

794 **Figure 4**. Sensitivity and specificity for level of CMR training. * denotes

795 statistically significant difference (p< 0.001) between sensitivity values. **

796 denotes statistically significant difference (p< 0.001) between specificity

797 values.

798 Sens: sensitivity, spec: specificity.

799

800 **Figure 5**. Percentage of correct identification of CAD (diagnostic accuracy)

801 using stress perfusion only or stress and rest images.

802 CAD: coronary artery disease.

803

804   **Figure 6**. CAD classification for different levels of CMR training.

805   CAD: coronary artery disease, 1VD: one-vessel disease, 2VD, two-vessel

806   disease, 3VD: three-vessel disease.

807