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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 **Keywords**

171 Cardiovascular Magnetic Resonance, Stress Perfusion Imaging, Coronary  
172 Artery Disease, Quantitative assessment, Myocardial Ischemia, Diagnostic  
173 Accuracy, Training.

174

175 **Abbreviation list**

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

264 **Operator selection**

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

282

283 **Image analysis - visual assessment**

284 Each operator was asked to report each of the 53 scans twice over a 4-week  
285 period, with a minimum interval of 2 weeks between first and second read.  
286 The scans were anonymized and presented to the operator as a full dataset,  
287 including stress and rest perfusion and LGE, or as reduced datasets,  
288 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 transmural 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 ( $86.5 \pm 6.1\%$ )  
371 and low specificity ( $41.9 \pm 10.9\%$ ). Level-2 operators had a sensitivity of  
372  $57.3 \pm 4.7\%$  and a specificity of  $69.4 \pm 9.9\%$ . Level-3 operators showed a  
373 sensitivity of  $71.9 \pm 13\%$  and a specificity of  $88.7 \pm 6.7\%$  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 ( $69.6 \pm 14.3\%$  vs  $67.1 \pm 13.1\%$ ;  $p = 0.34$ ). 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

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 **Conclusions**

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

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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  
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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.

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609 **Endnotes:** Not applicable.

610

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- 778



779 **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