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**ORIGINAL PAPER**

# Sex- and age-specific normal values for automated quantitative pixel-wise myocardial perfusion cardiovascular magnetic resonance

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**See the editorial comment for this article 'Quantitative myocardial blood flow assessment using stress cardiac magnetic resonance: one step closer to widespread clinical adoption', by A.R. Patel and C.M. Kramer, https://doi.org/10.1093/ehjci/jeac263.**

**Aims** Recently developed in-line automated cardiovascular magnetic resonance (CMR) myocardial perfusion mapping has been shown to be reproducible and comparable with positron emission tomography (PET), and can be easily integrated into clinical workflows. Bringing quantitative myocardial perfusion CMR into routine clinical care requires knowledge of sex- and age-specific normal values in order to define thresholds for disease detection. This study aimed to establish sex- and age-specific normal values for stress and rest CMR myocardial blood flow (MBF) in healthy volunteers.

**Methods and results** A total of 151 healthy volunteers recruited from two centres underwent adenosine stress and rest myocardial perfusion CMR. In-line automatic reconstruction and post processing of perfusion data were implemented within the Gadgetron software framework, creating pixel-wise perfusion maps. Rest and stress MBF were measured, deriving myocardial perfusion reserve (MPR) and were subdivided by sex and age. Mean MBF in all subjects was $0.62 \pm 0.13$ mL/g/min at rest and $2.24 \pm 0.53$ mL/g/min during stress. Mean MPR was $3.74 \pm 1.00$. Compared with males, females had higher rest ($0.69 \pm 0.13$ vs. $0.58 \pm 0.12$ mL/g/min, $P < 0.01$) and stress MBF ($2.41 \pm 0.47$ vs. $2.13 \pm 0.54$ mL/g/min, $P = 0.001$). Stress MBF and MPR showed significant negative correlations with increasing age ($r = -0.43$, $P < 0.001$ and $r = -0.34$, $P < 0.001$, respectively).

**Conclusion** Fully automated in-line CMR myocardial perfusion mapping produces similar normal values to the published CMR and PET literature. There is a significant increase in rest and stress MBF, but not MPR, in females and a reduction of stress MBF and MPR with advancing age, advocating the use of sex- and age-specific reference ranges for diagnostic use.

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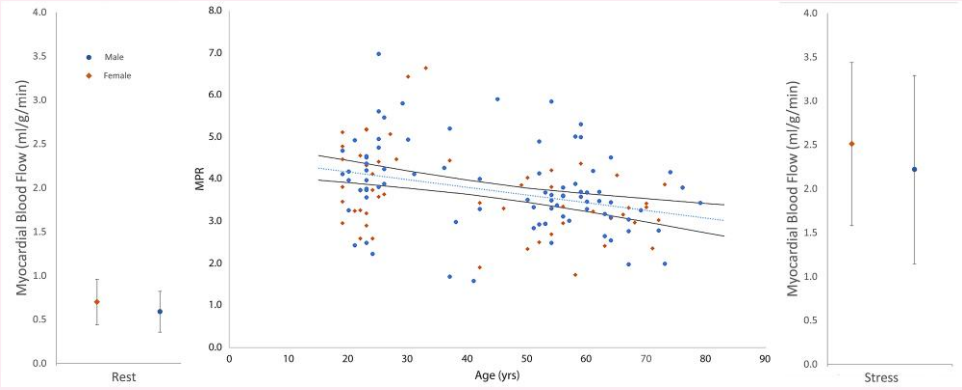
## Graphical Abstract




A total of 150 healthy volunteers underwent adenosine stress and rest quantitative perfusion cardiovascular magnetic resonance. Normal values were established in this large cohort with a wide age range. We demonstrated higher stress and rest myocardial blood flow in females compared with males, and a decrease in stress myocardial blood flow and myocardial perfusion reserve with increasing age. Suggested normal ranges referenced to age and sex have been created with this data.

**Keywords** normal values • myocardial perfusion • cardiovascular magnetic resonance • myocardial perfusion reserve

# Introduction

There is increasing evidence that clinical decision-making for patients with stable coronary artery disease (CAD) should be based on quantitative rather than visual assessment to determine the functional significance of coronary stenosis.[1–3] The invasive reference standard for functional assessment of coronary stenosis is fractional flow reserve (FFR), while positron emission tomography (PET) has been considered the reference standard for non-invasive quantitative assessment of myocardial blood flow (MBF) and myocardial perfusion reserve (MPR).[4] Cardiovascular magnetic resonance (CMR) myocardial perfusion imaging can also be used to estimate MBF and MPR and has shown good agreement in validation studies against microspheres,[5] PET,[6] and FFR.[7] The latest US guidelines for the management of chest pain give both quantitative perfusion CMR and PET a new 2a indication in stable patients with known CAD.[8] Compared with PET, CMR has the advantages of not exposing patients to ionizing radiation, more widespread availability, higher in-plane spatial resolution, and the ability to provide additional assessment of cardiac structure and function within the same study. However, in the past quantitative myocardial perfusion, CMR has required time-consuming, manual, offline processing, which restricted its use to expert centres and prevented wider clinical adoption. Recently, developed respiratory motion-corrected myocardial perfusion CMR with automated in-line perfusion mapping allows the generation of pixel-wise MBF maps[9] during free-breathing acquisition and without user interaction, and has been shown to provide comparable MBF and MPR values to PET both in assessment of CAD and in repeatability of measurements.[10,11] This method offers the enticing potential of making largely user independent quantitative myocardial perfusion analysis available in routine clinical care.

Adoption of the method in clinical practice requires the definition of a specific range of normal values. This study looked to establish sex-specific normal values for CMR myocardial perfusion mapping in healthy volunteers and over a wide age range, representative of patients seen in clinical care.

# Methods

## Study population

A total of 151 healthy volunteers with no history of cardiac disease or major risk factors were recruited in two cardiac centres (Leeds Teaching Hospitals Trust, Leeds, UK and University Hospitals of Leicester NHS Trust, Leicester, UK). Exclusion criteria included a known history of arterial hypertension, hypercholesterolaemia, diabetes mellitus, smoking, previous CAD or revascularization or perfusion defect on the stress CMR, contraindications to adenosine, gadolinium-based contrast or MRI, and subsequent evidence of abnormal late gadolinium enhancement (LGE) on MRI.

## Study protocol

All scans were performed at 3 Tesla [Prisma (Leeds) or Skyra (Leicester), Siemens Healthcare, Erlangen, Germany] according to a standard protocol including cine imaging, adenosine stress and rest perfusion, and LGE. Patients were asked to abstain from caffeine for 24 h before the scan.

Pharmacological stress was achieved with adenosine infusion at 140 μg/kg/min for a minimum of 3 min. The dose was increased to a maximum of 210 μg/kg/min after 2 minutes if there was insufficient symptomatic or haemodynamic response, defined as a heart rate (HR) increase of less than 10 bpm.[12] Volunteers were monitored for symptoms (e.g. flushing, dyspnoea, chest pain) throughout the scan. Blood pressure (BP) and HR were recorded during adenosine infusion. An intravenous bolus of 0.05 or 0.075 mmol/kg of gadolinium-based contrast was administered for stress and rest perfusion.

Survey images were followed by vertical and horizontal long axis images to plan the short-axis view for perfusion imaging in three slice positions (base, mid, and apex). Data acquisition used a multi-slice, free-breathing, saturation recovery pulse sequence with fast low-angle shot (FLASH) readout, acquired over 60 heartbeats. In the first three beats, proton density weighted images (without saturation preparation) were acquired. Arterial input function (AIF) data were obtained from interleaved low-resolution images (dual-sequence method) in a single slice positioned in the basal

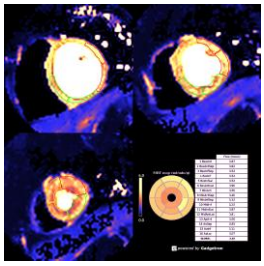


**Figure 1** Contouring of perfusion maps and segmental myocardial blood flow. Sixteen segment AHA contours were generated with values of individual segments average to calculate mean myocardial blood flow.

left ventricle (LV) with dual-echo acquisition to allow correction of T2*-related signal loss.[9]

After stress perfusion, a cine data set covering the heart in short-axis orientation was acquired after return of HR to baseline levels, followed by rest perfusion images, obtained using the same contrast and acquisition regime as for stress perfusion.

## In-line processing and quantitative analysis of perfusion data

In-line automatic reconstruction and post processing of perfusion data were implemented within the Gadgetron software framework.[9,13] Images were motion corrected and then corrected for surface coil intensity variation based on the proton density–weighted images. Signal intensity data were converted to gadolinium concentration based on automatically generated look-up tables. AIF data were extracted from the low-resolution gadolinium concentration images using automated segmentation of the LV cavity. MBF was calculated on a pixel-wise basis in the high-resolution images by blood tissue exchange model constrained deconvolution incorporating estimation of the delay time between bolus arrival in the LV cavity and the tissue of interest.[9] Automatic segmentation of the LV cavity and myocardium was performed by an artificial intelligence tool, excluding myocardial fat and papillary muscles. The AHA segmentation model was then further delineated and segmental MBF was calculated automatically as an average of all pixels[14] (*Figure 1*). Perfusion maps were visually inspected for quality control and discarded if there were errors. Values for each of the AHA 16 segments were recorded for stress and rest MBF, and global values were calculated as an average of these. Segments including LVOT or significant artefact were excluded from analysis.

Rate pressure product (RPP) was calculated for each perfusion acquisition (HR × systolic BP). Rest MBF values were corrected for RPP by dividing by the individual value for each patient and multiplying by 10 000 in keeping with previously established practice.[15]

MPR was calculated for each segment as stress MBF/rest MBF.

## Statistical analysis

Outliers were identified using the Tukey robust approach and removed from analysis if either<Q1 − 1.5 interquartile range (IQR) or >Q3 + 1.5IQR, proposed normal ranges were described as the 95% cohort range, using previously published methods.[16]

Age- and sex-matched samples were compared between centres and between Gadolinium-contrast dosing to ensure that they could reasonably be combined as a study population.

Analysis was performed using SPSS 23 (IBM, NY, USA). The Shapiro–Wilk test was used to assess normality of data. Data are presented as mean ± SD or median (IQR). Groups were compared using independent *t*-test if parametric or Mann–Whitney *U* test for non-parametric variables. Differences between coronary territories were compared using repeated measures analysis of variance. Coefficient of variation (CV) was calculated as SD/mean as a standardized measurement of dispersion to allow comparison with other studies. Correlation was assessed using Pearson's correlation coefficient. All statistical tests were two-tailed and $P < 0.05$ was considered significant.

# Results

One hundred and fifty-one volunteers were recruited and underwent adenosine stress CMR as described above.

A total of 150 volunteers were included in the final analysis. One set of data was excluded due to poor quality of data relating to arrhythmia during the scan. Five volunteers only had either stress or rest perfusion data available and a further nine results were classed as outliers (six rest and three stress MBF) and excluded. Remaining single MBF results were included in analysis without MPR. Age ranged from 19 to 79 years, with a median age of 49 (IQR 24–59) and 62 (41%) females.

One hundred and four patients were recruited from Leeds and 46 from Leicester with no significant difference in sex distribution between the two groups. Twenty patients received 0.075 mmol/kg contrast dosing, and the remainder had 0.05 mmol/kg. Using age- and sex-matched samples, there was no significant difference between stress or rest MBF measurements either between the two centres or when using 0.05 and 0.075 mmol contrast agent boluses (Supplementary material online, *Appendix S1*).

Haemodynamic data and response are seen in *Table 1*. Mean HR and RPP were significantly higher at stress than rest ($P < 0.001$).

## Myocardial blood flow

Mean MBF at rest and stress was 0.62 ± 0.13 and 2.24 ± 0.53 mL/g/min, respectively. Mean MPR was 3.74 ± 1.00. Mean RPP-corrected rest MBF was 0.83 ± 0.21 mL/g/min.

When coronary artery territories were compared, both rest and stress flow were highest in the left anterior descending (LAD) artery territory, with significant differences between the three territories (*Table 2*). Mean stress and rest MBF measured on a segmental basis were highest in AHA Segment 1 (basal anterior) 2.63 ± 0.73 and 0.69 ± 0.12 mL/g/min, and lowest in Segment 15 (apical inferior) 1.90 ± 0.46 and 0.53 ± 0.12 mL/g/min, respectively. Full data for all segments are provided in Supplementary material online, *Appendix S2*.

## Sex

Haemodynamic and MBF values divided by sex are given in *Tables 1* and *3*.

Both resting and stress HR, and rest and stress MBF were significantly higher in females compared with males (*Figure 2*). The absolute increase in HR and RPP between rest and stress was also significantly higher in females (*Table 1*). Rest RPP correlated with rest MBF ($r = 0.41$, $P < 0.001$); therefore, values of rest MBF corrected for RPP were calculated. Corrected resting MBF remained significantly higher in females (*Table 3*).

No significant difference was seen in MPR between sexes.

## Age

Increasing age negatively correlated with stress MBF ($r = -0.434$, $P < 0.001$) and MPR ($r = -0.339$, $P < 0.01$). No correlation was seen between age and rest MBF (*Figure 3*).

Rest RPP correlated with age ($r = 0.247$, $P = 0.004$); when rest MBF was corrected for RPP, there was a negative correlation with age ($r = -0.337$, $P < 0.001$; *Figure 3*).

**Table 1 Haemodynamic characteristics of participants**

| | All 150 | Male 88 | Female 62 | *P*-value (M:F) |
|---|---|---|---|---|
| Age (years) | 49 (24–59) | 52 (25–59) | 35 (23–57) | 0.105 |
| Rest HR (b.p.m.) | 63 ± 9.5 | 62 ± 9.5 | 65 ± 9.3 | 0.111 |
| Rest BP (mmHg) | 122 ± 19 | 124 ± 17 | 119 ± 20 | 0.111 |
| Rest RPP (mmHg, b.p.m.) | 7775 ± 1733 | 7765 ± 1646 | 7791 ± 1880 | 0.935 |
| Stress HR (b.p.m.) | 91 ± 17 | 86 ± 14 | 98 ± 18 | <0.001 |
| Stress BP (mmHg) | 123 ± 17 | 125 ± 17 | 120 ± 18 | 0.118 |
| Stress RPP (mmHg, b.p.m.) | 11 189 ± 2609 | 10 777 ± 2371 | 11 778 ± 2836 | 0.027 |
| Change HR (b.p.m.) | 26 ± 12 | 23 ± 11 | 31 ± 13 | <0.001 |
| Change BP (mmHg) | 1.5 ± 9 | 1.3 ± 9 | 1.7 ± 10 | 0.800 |
| Change RPP (mmHg, b.p.m.) | 3270 ± 1753 | 3005 ± 1649 | 3692 ± 1846 | 0.029 |

Values are given as median (interquartile range) or mean (±SD). The *P*-value denotes significance between sexes.
BP, systolic blood pressure; HR, heart rate; RPP, rate pressure product.

**Table 2 Global and coronary artery territory MBF in healthy volunteer population**

| | Rest MBF (mL/g/min) | | Stress MBF (mL/g/min) | | MPR | |
|---|---|---|---|---|---|---|
| | Mean | CV (%) | Mean | CV (%) | Mean | CV (%) |
| Global | 0.62 ± 0.13 | 20.9 | 2.24 ± 0.53 | 23.6 | 3.74 ± 1.00 | 26.7 |
| *Coronary territories* | | | | | | |
| LAD | 0.67 ± 0.15 | 22.5 | 2.36 ± 0.57 | 24.2 | 3.63 ± 0.96 | 26.4 |
| Cx | 0.59 ± 0.14 | 23.7 | 2.25 ± 0.56 | 24.9 | 3.95 ± 1.17 | 29.6 |
| RCA | 0.59 ± 0.12 | 20.2 | 2.10 ± 0.50 | 23.8 | 3.66 ± 0.98 | 26.8 |
| | *P* < 0.001 | | *P* < 0.001 | | *P* < 0.001 | |

CV, coefficient of variation; Cx, circumflex; LAD, left anterior descending; MBF, myocardial blood flow; MPR, myocardial blood flow; RCA, right coronary artery.

Normal ranges for MBF and MPR, with 95% confidence intervals are shown in *Figure 4*.

# Discussion

This study reports the largest normal range of MBF and MPR for myocardial perfusion CMR in healthy volunteers, acquired with automated in-line perfusion mapping. We present the first normal values for quantitative myocardial perfusion CMR stratified by age and sex.

## Global MBF

Previously published normal ranges of MBF and MPR obtained using PET and CMR (*Table 4*) illustrate the range of values obtained with these methods. Previous CMR studies have reported rest MBF values between 0.76 ± 0.1 and 1.24 ± 0.19 mL/g/min.[19,20] The results from the current study are at the lower end of this range.

Reported rest MBF in PET has varied depending on the PET tracer,[29,30] kinetic model,[31] and methodology[32] used. The large number of confounders makes comparison between published data and modalities challenging. Values have ranged from 0.62 ± 0.14 to 1.10 ± 0.2 mL/g/min.[23,24] The most recent PET studies including healthy volunteers have reported rest MBF of 0.68 ± 0.2[33] and 0.71 ± 0.11 mL/g/min,[19] both more similar to our results.

**Table 3 Myocardial blood flow and perfusion reserve values in different sexes**

| | All | Male | Female | *P*-value (M:F) |
|---|---|---|---|---|
| *N* | 150 | 88 | 62 | |
| Rest MBF | 0.62 ± 0.13 | 0.58 ± 0.12 | 0.69 ± 0.13 | <0.001 |
| Stress MBF | 2.24 ± 0.53 | 2.13 ± 0.54 | 2.41 ± 0.47 | 0.001 |
| MPR | 3.74 ± 1.0 | 3.79 ± 1.0 | 3.67 ± 1.0 | 0.522 |
| RPP corrected rest MBF | 0.83 ± 0.21 | 0.77 ± 0.18 | 0.92 ± 0.21 | <0.001 |

Values are given as mean (±SD). MBF is given in mL/g/min. *P*-values are given for difference between sexes.
MBF, myocardial blood flow; MPR, myocardial blood flow; MPR (corrected rest values), uncorrected stress MBF/corrected rest MBF; RPP, rate pressure product.

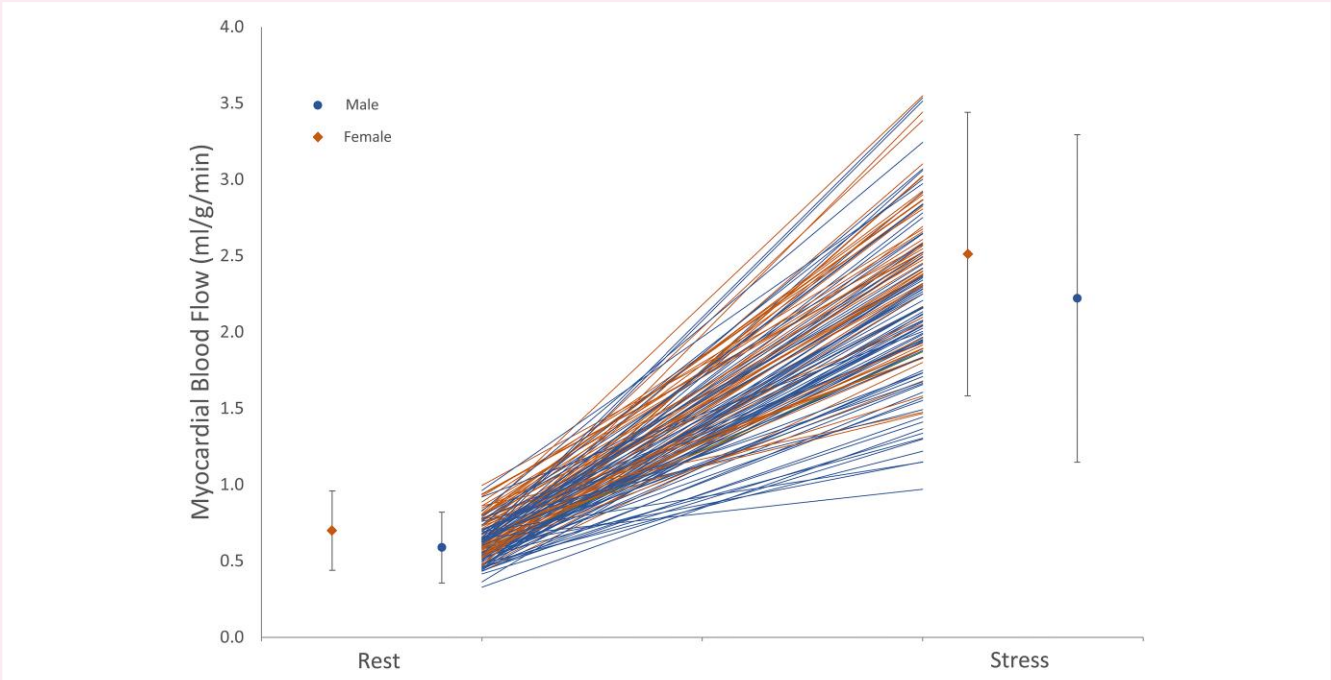



**Figure 2** Rest and stress MBF in both sexes. Global myocardial blood flow was significantly lower in males both at rest (0.58 ± 0.12 vs. 0.69 ± 0.13 mL/g/min, $P < 0.001$) and during adenosine stress (2.13 ± 0.54 vs. 2.41 ± 0.47 mL/g/min, $P = 0.001$).

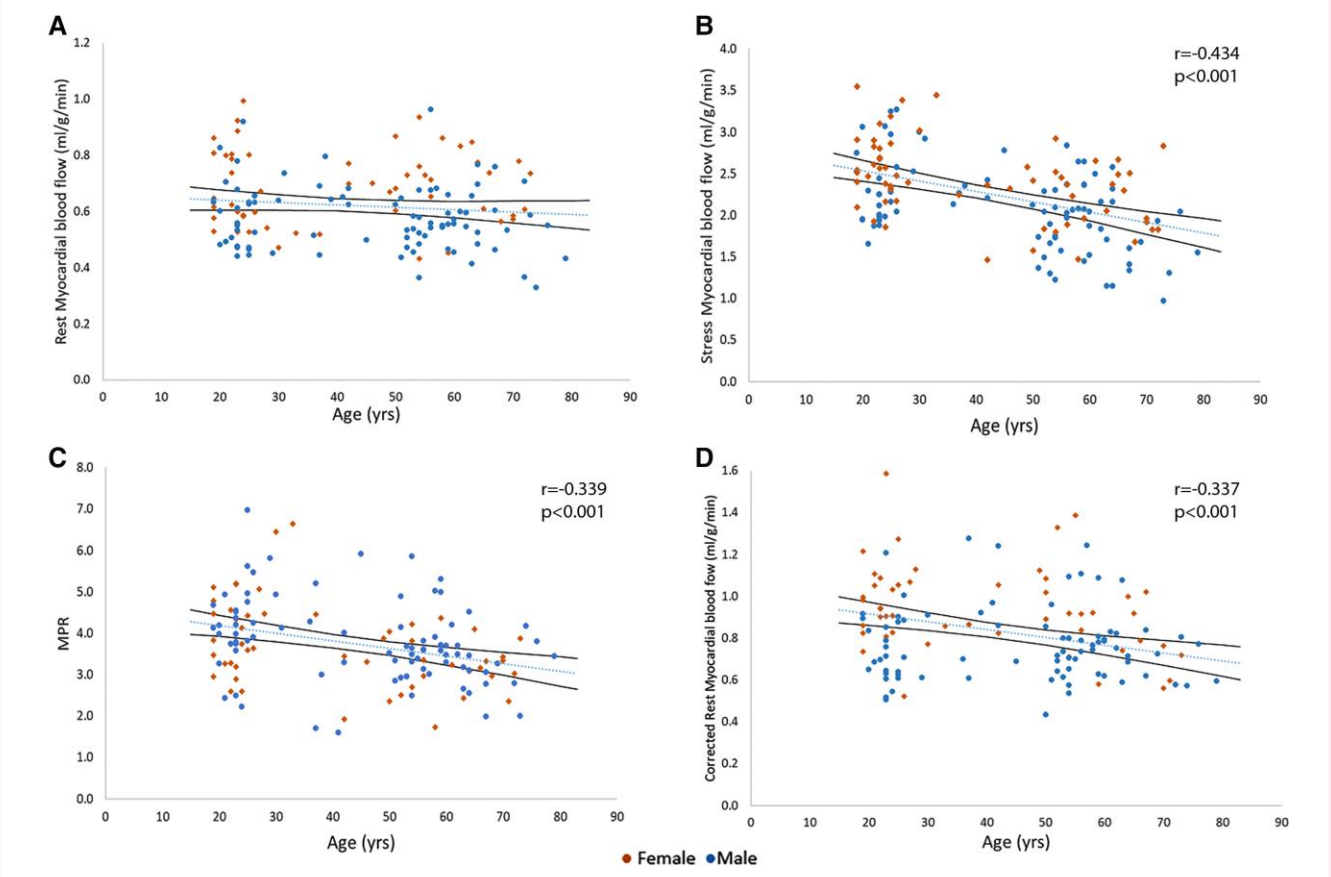



**Figure 3** Correlations between MBF, MPR, and age. Rest MBF (*A*) shows no correlation between MBF and age. Stress MBF (*B*) and MPR (*C*) demonstrate a signficant negative correlation with age. Rest MBF corrected for RPP (*D*) demonstrates a signifcant correlation with age.

Stress MBF by CMR has been reported to vary from 2.78 ± 0.61 to 4.50 ± 0.91 mL/g/min in previous smaller studies.[17,20] Within PET studies, a wider range of normal values have been reported ranging from 1.97 ± 0.45 to 4.40 ± 0.9 mL/g/min.[23,24] Our results are comparable with the larger of these previous studies.

Previous values of MPR with CMR have ranged from 2.7 ± 0.3 to 4.2 ± 1.0[17,22] and PET values have varied between 3.75 ± 1.24 and 4.46 ± 1.43.[19,27] The findings in the current study are in keeping with these previous values.

Both stress MBF and MPR values have merit in assessing ischaemia. In our study, MPR showed greater variability between individuals than absolute stress values, which was expected as MPR is calculated as the ratio of two parameters, compounding variability from both of its constituents. In clinical studies, stress MBF has accurately detected the presence of significant coronary stenosis, with comparable accuracy as MPR.[34,35] This, together with the better reproducibility of stress MBF demonstrated in both CMR and PET studies,[11,28] supports the use of stress MBF rather than MPR for the diagnosis of ischaemia when using

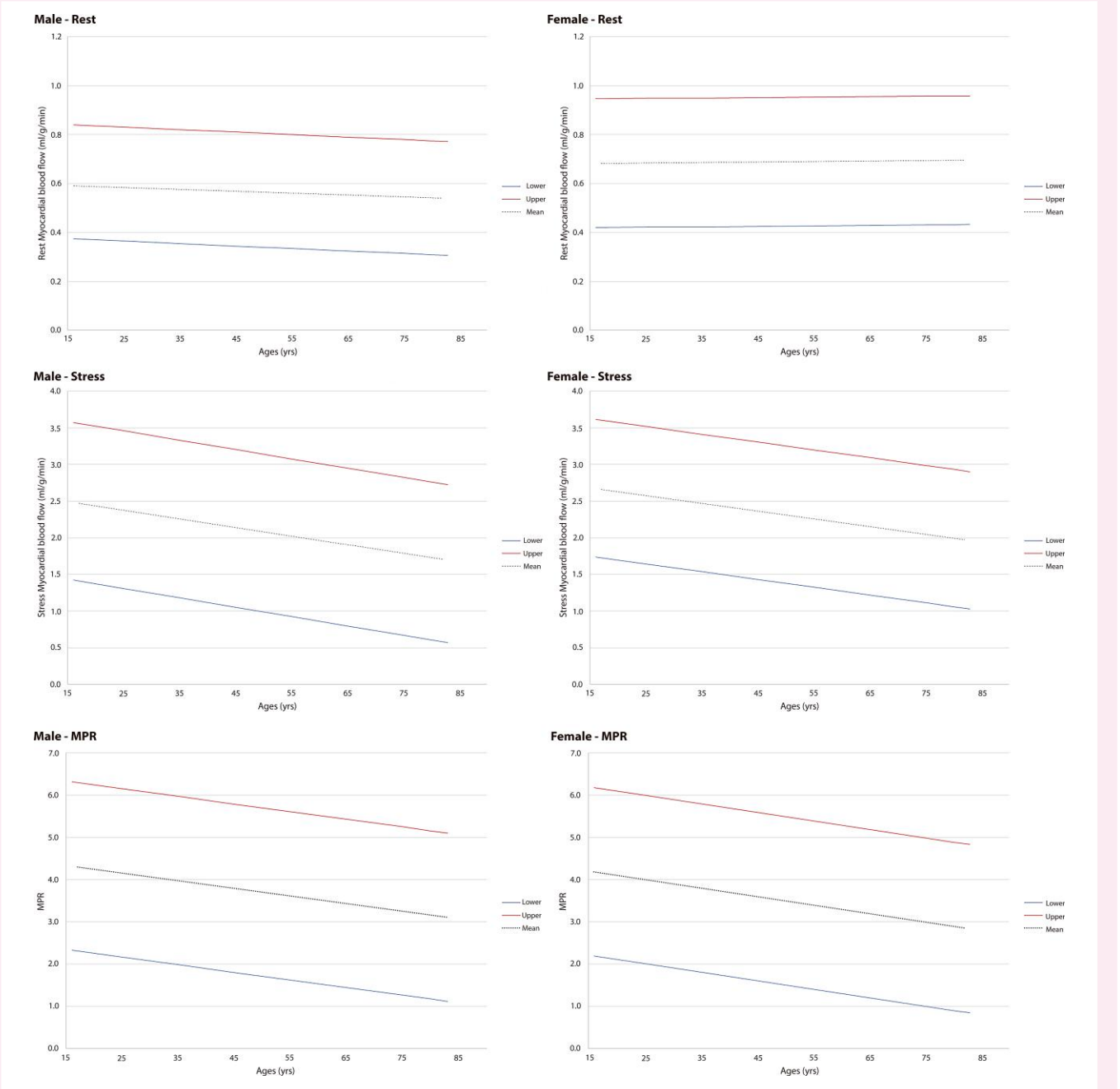



**Figure 4** Normal reference ranges for MBF and MPR. Figures show mean values and the 95% confidence interval for the range, allowing for changes related to age.

**Table 4 Summary of previous published data with larger groups of healthy volunteers**

| Author | Year | n | Mean age | Rest MBF (mL/g/min) | CV (%) | Stress MBF (mL/g/min) | CV (%) | MPR | CV (%) |
|---|---|---|---|---|---|---|---|---|---|
| CMR | | | | | | | | | |
| Vasu[17,a] | 2013 | 15 | 21 | 1.04(±0.24) | 23 | 2.78(±0.61) | 22 | 2.7(±0.3) | 11 |
| Fairbairn[18,b] | 2014 | 19 | 22 ± 4 | 0.97(±0.4) | 41 | 3.4(±1.2) | 35 | | |
| Tomiyama[19,c] | 2015 | 20 | 28 ± 9 | 0.76(±0.1) | 13 | 3.04(±0.82) | 27 | 4.13(±1.33) | 32 |
| Motwani[20,b] | 2015 | 30 | 22 ± 2 | 1.24(±0.19) | 15 | 4.5(±0.91) | 20 | 3.63(±0.95) | 26 |
| Knott[21,d] | 2019 | 24 | 37 | 0.86 | | 3.07 | | | |
| Nickander[22,d] | 2020 | 41 | 26 ± 5 | 0.88 ± 0.19 | 22 | 3.62 ± 0.71 | 20 | 4.2 ± 1.0 | 24 |
| PET | | | | | | | | | |
| Chan[23] | 1992 | 20 | 34 ± 16 | 1.10(±0.2) | 18 | 4.40(±0.9) | 20 | | |
| Nagamachi[24] | 1996 | 21 | 34 ± 15 | 0.62(±0.14) | 23 | 1.97(±0.45) | 23 | | |
| Muzik[25] | 1998 | 20 | 44 ± 11 | 0.67(±0.11) | 17 | 2.85(±0.49) | 17 | 4.28(±0.65) | 15 |
| Kaufmann[26] | 2000 | 61 | 45 ± 7 | 0.87(±0.14) | 16 | 3.63(±1.02) | 28 | 4.23(±1.29) | 30 |
| Chareonthaitawee[27] | 2001 | 169 | 46 ± 12 | 0.99(±0.23) | 23 | 3.54(±1.01) | 29 | 3.75(±1.24) | 33 |
| Sdringola[28] | 2011 | 107 | 29 ± 5 | 0.70(±0.15) | 21 | 2.75(±0.58) | 21 | 4.03(±0.84) | 21 |
| Tomiyama[19] | 2015 | 20 | 28 ± 9 | 0.71(±0.11) | 15 | 3.09(±0.97) | 31 | 4.46(±1.43) | 32 |
| Combined | | 567 | 36 | 0.89 | | 3.32 | | 3.92 | |
| This study | 2021 | 150 | 44 | 0.62(±0.13) | 25 | 2.24(±0.53) | 26 | 3.74(±1.00) | 29 |

Values are expressed as mean(±SD). CV is calculated as SD/mean*100(%) for ease of comparison between studies.
CMR, cardiac magnetic resonance; CV, coefficient of variation; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; PET, positron emission tomography.
CMR quantitative perfusion methodology:
[a]Fully quantitative model constrained devolution.
[b]Fermi constrained devolution.
[c]Single compartment model.
[d]Dual sequence model, BTEX constrained. All used single gadolinium bolus.

a single method of MBF quantification, with additional benefits of a shorter acquisition protocol and simpler analysis. When evaluating between modalities and methods, however, MPR may be a more useful comparator, minimizing the effect of different reference ranges between techniques—as seen in published studies (*Table 4*), the range of MPR seen in normal volunteers is considerably lower than that in either stress or rest MBF.

## Regional MBF

We have demonstrated higher resting MBF within the LAD territory compared with the other coronary territories. This finding is consistent with some, but not all, of the previous literature. PET data are usually interpreted on a segmental basis, dividing the myocardium into four quadrants (anterior, lateral, inferior, and septal). One large study ($n = 169$) showed a significant difference in corrected rest MBF between regions, which was due to higher flow in the anterior (1.44 ± 0.41 mL/g/min) and lateral segments (1.41 ± 0.39 mL/g/min), both attributable to the LAD territory vs. the inferior segment (1.23 ± 0.32 mL/g/min, $P < 0.001$ for both).[27]

Several other PET studies have shown highest flow values in the anterior and lowest values in the inferior segments but have not undertaken statistical comparison.[28,36,37] Conversely, several other studies have shown no significant difference between regions,[24,38,39] including previous CMR studies,[20] this is likely related to the relatively small sample sizes in these studies ($n = 8$–30).

We also provide data on regional blood flow and MPR in AHA segments (Supplementary material online, *Appendix S2*). To the best of our knowledge, segmental MBF for all 16 segments has not previously been published. These values have been provided as they may be integrated in future analysis algorithms for the diagnosis of coronary disease. While there is slightly more variance in values of segmental flow, as may be expected when comparing data from smaller regions, CV for both stress and rest MBF was <30% at segmental level.

## Sex

Multiple studies have shown differences in MBF between sexes, consistently showing MBF at rest to be higher in females, as in our data. This has been seen in both large CMR and PET studies including a multi-ethnic study of atherosclerosis (MESA) substudy of 222 asymptomatic patients, and a PET study of 169 healthy volunteers, supported by other smaller and more recent data.[22,27,40–42]

Invasively measured coronary flow has also been reported to show sex differences. In a study of 28 patients with angiographically normal coronary arteries, coronary flow indexed to LV mass was higher in females (0.996 ± 0.236 vs. 0.854 ± 0.337 mL/g), although this difference was not assessed for significance.[43]

We have also demonstrated a heightened haemodynamic response to adenosine, and an increased stress MBF in females compared with males, findings that have been previously reported in studies with larger proportions of female participants.[22,40,41] One large PET study showed no significant difference in hyperaemic blood flow between sexes, but the proportion of females was only 22%, limiting the study's ability to differentiate reliably between sexes. Others have shown no significant difference between MBF in both sexes at either rest or stress.[15,44] Our findings are in keeping with the previous studies that showed higher MBF at both stress and rest and an increased physiological response

to pharmacological stress in females. The underlying cause for this difference is unclear. Although females had higher resting HR, when we corrected MBF for either HR or RPP, a significant difference remained and other mechanisms such as oestrogen levels, which can mediate coronary tone, or increased myocardial capillary density in females may be at play.[45,46] However, in the MESA study,[40] correction of MBF for menopause status and hormone use did not remove differences in MBF between the sexes. The studies we quote that have compared MBF and seen no difference between the sexes comprise relatively small numbers ($n = 22$[15] and $n = 14$[44]). It is likely that intrinsic variability of MBF requires larger numbers to establish significant difference between groups.

Regardless of the mechanisms, the observed differences in rest and stress MBF support the use of separate normal ranges for the sexes, narrowing the limits compared with a less homogeneous group.

## Age

We have shown a decrease in both stress MBF and MPR with age, while no difference was seen in absolute rest MBF, there was a decline in RPP-corrected rest MBF with age. The findings are consistent with previous studies showing lower values in older age groups,[47] or a decline in stress MBF with age.[27,40,42] Findings from the MESA substudy reported increasing RPP with age, a correlation that we have also demonstrated, suggesting a higher level of cardiac work required to maintain the same resting flow. No related correlation was seen between RPP at stress, potentially demonstrating a blunted stress response in age which is likely multifactorial including adenosine response and change in vascular structure and function associated with age. The correlations support the use of age-related values when establishing normal ranges. The values for stress MBF in this study are at the lower end of those previously published, and it may be that the inclusion of a larger proportion of older volunteers accounts for some of this difference (23% over 60 and 7% over 70).

## Study limitations

All normal data sets of values for MBF are influenced by physiological variation as well as variation within the model and analysis. While we aimed to minimize physiological effect as much as possible, not all factors may have been controlled for. Although we advised our volunteers to avoid caffeine for 24 h prior to the scan, previous studies have demonstrated that up to 20% may still have detectable caffeine levels.[48] We can however be confident that adequate stress was achieved through clinical monitoring and haemodynamic response to the adenosine dosing protocol. Volunteers did not undergo coronary angiography; therefore, some may not have been truly normal. We aimed to mitigate this potential limitation by excluding any subject with regional perfusion defects. All studies were performed using a FLASH pulse sequence and one a single vendor platform and results for MBF may vary using other pulse sequences and scanner manufacturers.

# Conclusion

Quantitative CMR myocardial perfusion mapping produces values similar to those of the reference method PET and with a similar degree of variation. There is a significant increase in rest and stress MBF in females and a reduction of stress MBF and MPR with advancing age, advocating the use of sex- and age-specific reference ranges for diagnostic use.

# Supplementary material

Supplementary materials are available at *European Heart Journal – Cardiovascular Imaging* online.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**Conflict of interest:** None declared.


## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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