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ORIGINAL RESEARCH ARTICLE

Normal perfusion and function myocardial perfusion imaging indices in Iranian normal females

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ABSTRACT

Introduction: Normal population data is necessary for the quantification of myocardial perfusion studies (MPS). In Iran, data embedded in the Cedars Cardiac Suite, from young Californian volunteers, is used. We generated an Iranian female dataset and compared it with the original one.
Methods: Thirty-one females aged 20-45 years without coronary artery disease risks were recruited. They underwent two-day exercise stress (Bruce protocol) and rest gated SPECT MPS. [^{99m}Tc]Tc-MIBI was injected (15 mCi) and imaging for stress and rest phases were started 60 and 90 min later, respectively, in supine and prone positions. A dual head gamma camera was used, ProSPECT (PNP, Tehran, Iran). Polar plots were extracted and a normal database generated.
Results: Visually, none of the participants presented a reversible perfusion defect. Index for transient ischemic dilation was 1.1±0.15 and 1.1±0.14, respectively for prone and supine positions; lung heart uptake ratio 0.3±0.1 and 0.28±0.1; ejection fraction 69.8±7.8 and 70±8; peak filling rate 2.9±0.75 and 2.9±0.95 end-diastolic volume/sec; and time to peak filling rate at 178±44.5 and 203±49.5 millisecond. Compared to the original prone Californian normal database, total perfusion defect for stress and rest was 12.1±6.7 and 5.3±5.2, and for the supine position 10.1±0.5.4 and 4.0±3.4, respectively.
Conclusion: Iranian normal database for MPS was generated with a remarkable difference from the original normal data.

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INTRODUCTION

Myocardial Perfusion Scan (MPS) is a noninvasive method for evaluation of myocardial cell surface perfusion, the endpoint which is subject to decrease after coronary artery disease (CAD) [1-3]. For the interpretation of MPS, the visual assessment is the cornerstone, but the quantification and comparison with normal data are indispensable [4, 5]. There is various software with imbedded data from a normal population, the most commonly used include Cedars Cardiac Suite (Cedars-Sinai Medical Center, Los Angeles, CA) [6], Emory toolbox (Emory University, Atlanta, GA, USA), and 4DM (University of Michigan Medical Center, Ann Arbor, MI, USA) [7, 8]. These data are acquired from participants without CAD or with very low CAD risk at the center the software has been developed, hence plausibly from the population living in that area.

There is evidence that the normal data differs between populations, and the use of a predetermined database may cause diagnostic problems [8]. Certain variables may contribute to the difference between predetermined software's data and the normal data from the population the MPS is done; these variables include differences in the anthropometric characteristics, fine image acquisition specifications, and radiopharmaceutical determinants between two settings [9]. Before reliance on the normal database of the software, it is prudent to assess the possible variation between the software's normal database and the normal data of the population MPS is acquired. Were the embedded data remarkably differed from the normal results of the population, the normal database should be corrected. Many populations including Japan, Spain, and China have already developed their normal databases [10-12].

In the current study we are reporting the results of young women without CAD and with low CAD risk in an Iranian population, and discuss the deviation from the normal population embedded in Cedars Cardiac Suite generated in Cedars Sinai comprising Californian normal population data.

METHODS

After ethics committee approval invitations were posted in 10 academic public places scattered through Tehran including faculty, university hospitals, and campus. Also, an invitation was posted on Instagram. A 30$ bonus was provided, and inclusion criteria, the imaging protocol, and radiation risk were defined. Particularly, it was stated that almost an added cancer risk of smoking a usual cigarette every other day would be imposed on the participants due to two-day imaging with an accumulative dose of 30 mCi at about 5 mSv. The participants were interviewed for past medical history, and physical examination was done when appropriate. The study protocol was defined and written informed consents were collected. The participants were required to present 2 consecutive days within a week in our department.

Thirty-one 20-45 years old healthy women participated from Feb 2019 to Jan 2020. We aimed to include 30, but 31 were studied for possible nonparticipation and to compensate for missing data. For all except 2, the rest phase was done first with stress imaging the following day. Fifteen mCi [^{99m}Tc]Tc-MIBI (Pars Isotope, Tehran, Iran) was prepared according to manufacture instructions and injected via an IV line. The stress was done by exercise tolerance test (ETT) according to Bruce protocol up to stage 4 when radiopharmaceutical injection was done; exercise was continued at least 2 minutes after injection. In the rest phase 20 minutes after radiopharmaceutical administration, participants were instructed to ingest 150-200 gr cream (30% fat). Rest and stress images were acquired at 115±15 min and 40±20 min, respectively. Imaging was done by a cardiac dedicated dual head gamma camera (ProSPECT, Parto Negar Persia, Tehran, Iran). Images with another gamma camera (ADAC Forte, Philips, Milpitas, CA) was also acquired for visual assessment but results are not reported. The following specifications were used: semicircular imaging (right anterior oblique to left posterior oblique), 32 projections, 25 sec projection time, 64×64 matrix size, and cardiac gating with 8 frames. Imaging was done at both supine and prone positions and repeated for certain participants due to the presence of motion and extra cardiac activity.

Cinematic images were reviewed for quality control. Image processing was done using Cedars Cardiac CSI 2013.1, using iterative reconstruction (i.e. modified ordered expectation maximization with 4 subsets and 8 iterations). Visual assessment for the detection of hypo-perfusion areas was done. The hypoactive area with at least 25% reduction of count compared to the most active segment of each myocardium was considered perfusion abnormality with exception of the basal septal segment which is acceptably hypoactive due to its membranous nature. Also, gated images were inspected to find abnormalities of motion and contractility. Two

experienced nuclear physicians made the final decision of “being normal” by consensus.
SPSS v19 was used for data collection; distribution of the perfusion and gating indices were analyzed, and the generation of graphs was done. Sum stress score (SSS), sum rest score (SRS), and sum difference score (SDS), as well as total perfusion defect (TPD), were used to assess the deviation of the participants’ data from the Cedars Cardiac Suite embedded normal database. For assessment of linear correlation, the coefficient of correlation (i.e. Pearson r) was calculated; and the differences with $p<0.05$ were considered significant. To provide a possible threshold for detection of abnormality of indices 5 or 95 percentile was calculated for perfusion indices including transient ischemic dilation (TID) and lung heart ratio (LHR) as well as for gating indices. Finally, data of participants were defined in the Cedars Cardiac Suite as a possibly more fitted normal database for future comparisons.

RESULTS

The exercise tolerance test and visual assessment of MPS for participants aged 28.6±8.2 were normal, but the mean SSS, SRS, and SDS were higher than 3 and stress TPD higher than 10% indicating ischemia and fixed defects in a majority of participants (Table 1). Of concern, the mean SSS were 8±5 and 9±5, at supine and prone positions respectively. Anterior wall (i.e. 3 segments), apical wall, and apical and mid segments of anterolateral wall had mean relative perfusion <70% and all other segments had perfusion >70%. Ejection fraction (EF), end-diastolic volume (EDV), peak filling rate (PFR), the mean filling rate at 1/3 diastole (MFR/3), and time to peak filling rate (TFR) are presented in Table 2. The normal distribution of perfusion and function indices are presented in Figure 1. The possible cut point for normal-abnormal perfusion and gating measures are provided in Table 3.

Table 1. Perfusion indices for healthy women Iranian participants

Perfusion index		Mean †	Median‡	Interquartile range
Supine	SSS	8±5	8(0-20)	4-10
	SRS	3±3	3(0-12)	1-5
	SDS	4±2	4(1-9)	3-6
	TID	1.04±0.15	1.07(0.69-1.38)	0.96-1.14
	Stress TPD	10±5	10(0-24)	7-14
	Rest TPD	4±3	4(0-15)	1-5
	LHR	0.29±0.09	0.31(0-0.4)	0.27-0.34
Prone	SSS	9±5	9(1-24)	5-11
	SRS	5±4	4(0-17)	2-7
	SDS	4±3	4(0-10)	2-6
	TID	1.09±0.16	1.11(0.72-1.45)	1.02-1.16
	Stress TPD	12±7	11(1-31)	6-15
	Rest TPD	5±5	4(0-21)	1-8
	LHR	0.3±0.09	0.3(0-0.39)	0.29-0.35

SSS: Sum stress score, SRS: Sum rest score, SDS: Sum difference score, TPD: Total perfusion defect, TID: Transient ischemic dilation (TID), LHR: Lung heart ration (LHR)
† data are mean ± standard deviation
‡ data are Median and range in parentheses

Table 2. Function (gating) indices for healthy women Iranian participants

Gating index		Mean †	Range	Interquartile Range
Supine	EF (%)	70±8	53-84	65-73
	PFR (EDV/sec)	2.9±0.75	1.58-4.74	2.43-3.24
	TFR (mSec)	178±44.3	51-275	155-201
	EDV (ml)	51±11	33-78	41-59
	MFR/3 (EDV/sec)	1.52±0.43	0.81-2.74	1.2-1.81
Prone	EF (%)	70±8	54-86	65-77
	PFR (EDV/sec)	2.88±0.95	1.22-5.29	2.31-3.46
	TFR (mSec)	203±49.4	68-303	180-240
	EDV (ml)	53±11	32-73	43-62
	MFR/3 (EDV/sec)	1.16±0.27	0.73-1.85	0.97-1.29

EF: Ejection fraction, EDV: End-diastolic volume, PFR: Peak filling rate, MFR/3: Mean filling rate at 1/3 diastole, TFR: Ttime to peak filling rate
† data are mean ± standard deviation

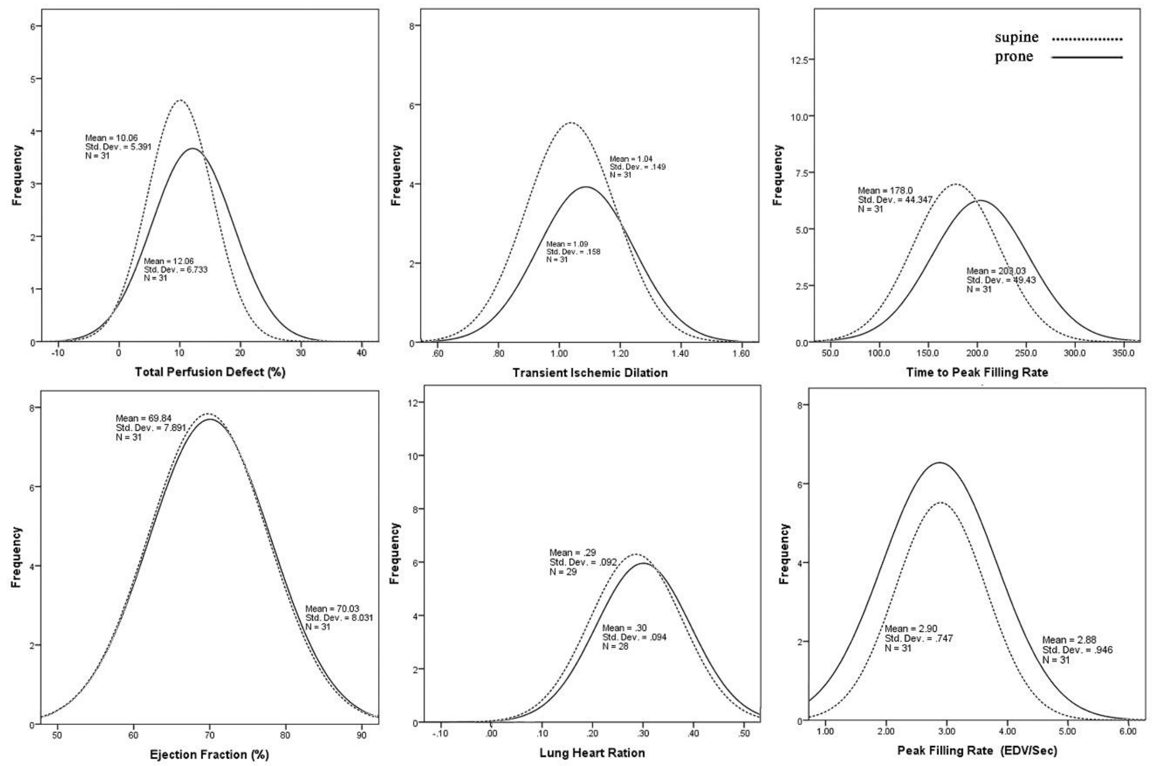

Fig 1. Normal distribution of perfusion and function indices.

(TPD: Total perfusion defect, TID: Transient ischemic dilation, TFR: Time to peak filling rate, EF: Ejection fraction, LHR: Lung heart ratio)

Table 3. The proposed threshold for abnormal measures (95 percentile)

position	EF (%)	EDV (ml)	PFR (EDV/sec)	TFR (mSec)	MFR/3 (EDV/sec)	TID	LHR
Supine	53.6	75	1.63	99.64	0.85	1.30	0.385
Prone	55.2	70	1.37	98.60	0.75	1.45	0.390

FE: Ejection fraction, EDV: End-diastolic volume, PFR: Peak filling rate, MFR/3: Mean filling rate at 1/3 diastole, TFR: Time to peak filling rate, TID: Transient ischemic dilation, LHR: Lung heart ration

There was significant correlation between certain indices as follows: PFR and EDV (inverse; P=0.01 and r= -0.58), PFR and EF (direct; P≤ 0.001 and r= 0.69), EDV and EF (inverse; P≤ 0.001 and r= -0.63), TID and PFR (inverse; P= 0.015 and r= -0.43) and TID and EDV (direct; P ≤ 0.01 and r=0.46).

DISCUSSION

High SSS and TPD highlight that either the MPS of normal Iranian women differs remarkably from those for normal Californian women embedded in the Cedars Cardiac Suite or the camera used in the current study has different imaging qualities compared to the original ADAC camera used to develop the Cedars software. This finding repeats the results by Nakazato et al. [13] in a similar pattern but contrasts with the results of the study by Nakajima et al. [8].The reason for these differences may comprise anthropometric variations between two populations but also indicates differences in imaging settings and camera properties.

Imaging setting differences include tracer, preparation variations, different injected doses, variable time lapse before imaging, fine changes in the exercise methods, and acquisition characteristics. The tracer we routinely use, and was used for the current study, is definitely different from that Cedars Cardiac Suite developers used when generating its normal database. The changes of injected dose and acquisition specifications including projection time and the number of stops may contribute to the differences.

In regard to the camera structures, it should be considered that the ProSPECT field of view, sensitivity and collimation as a cardiac dedicated camera are definitely different from the specifications of the variable angle dual head ADAC gamma camera used in original research.

While the sensitivity of the camera crystal decrements over time, when a relatively old camera is used in a developing country, the deviation of the indices from those generated at optimal factory settings should be held in mind. We used a brand new camera different from that used for the original Cedars Cardiac Suite.

Among all values, the SSS is particularly high at 8 and 9 at supine and prone positions, respectively, for normal young females. The lowest relative perfusion was allocated into the apex, anterior and distal anterolateral wall sections. The breast size and corresponding attenuation may justify high SSS in very low risk Iranian female population, the finding that we usually encounter in routine practice. Recent studies have shown some factors like gender, position, stress protocol, and tracer have a potential effect on the specification of normal perfusion limits; we consider them as well [14].

The nuclear physician relies on the visual finding and take the advantage of assistance from the quantification software as well as automates interpretations when available. Since we documented that the quantification software interpreted the normal participant's MPS as abnormal, the comparison of patients' MPS with the embedded normal database of the software-generated in a different population would definitely cause false-positive results.

The perfusion and function indices in the normal population of the current study replicate the figure in many previous studies. For example, the EF of women calculated at 53.6 at supine position is similar to previous studies [6, 7, 15]. Also, supine position LHR calculated at 0.39 is rather similar to many other studies [16, 17], but different from others [18]. The threshold for EDV and PFR were calculated at 75mL and 1.6 EDV/sec, respectively, which are plausible and similar to other reports [8], however different values are reported for Corridor 4DM SPECT studies [19]. Nevertheless, TFR we calculated at 267 mSec was rather higher than the normal expected values of lower than 200 mSec previously known [20]. Also, the TID threshold at 1.3 for exercise was well above the expected standard of 1.2. A similar finding for prone position was achieved which is not discussed in detail because the supine is considered the standard position.

The current study suffers from remarkable drawbacks; first, the sample size was limited. Second, the study includes females. Decision to study only on a gender was done to decrease the variations of the MPI indices due to anatomical gender difference. Third, Althogh, the study sample is selected from very low risk and potentially normal population, a few perfusion indices including SSS, SDS and SRS in the current research is determinedly higher than that of previously established range for normal population. This may be partly related to the differences between devices not merely resulted from the difference of populations. It merits a future study comparing two different devises to assess the device based acquisition differences. Lastly, 8 frame imaging was employed to replicate routine imaging for assessment of perfusion indices. It should be considered that gated SPECT indices including LVEF and volumes are not robust with 8-frame imaging as the 16-frame images are.

CONCLUSION

We conclude that the normal database embedded in Autocount software does not match the normal population of Iranian women, hence quantification for MPS should be skeptically reviewed in this context.

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