The Chinese cardiorespiratory and circulatory system at work in women and men: a case–control study

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Summary

Background The physiology of prominent prognostic factors in the cardiorespiratory system remains unchartered in the world's largest ethnic group: Hans Chinese (HC). This study assessed and contrasted the fundamental variables in HC and European-American (EA) individuals.

Methods Healthy HC and EA adults ($n = 140$, 43% ♀) closely matched by age, sex and physical activity were included. Body composition (DXA) and haematological variables (haemoglobin mass, blood volume (BV)) were measured at rest. Pulmonary O_2 uptake (VO_2) measurements along with cycle ergometry designed for accurate transthoracic echocardiography were implemented to assess cardiorespiratory structure/function up to peak effort.

Findings HC presented with higher body fat and lower lean body mass (LBM) percentage than EA irrespective of sex ($P \leq 0.014$). BV did not differ whereas blood haemoglobin concentration was lower in HC compared with EA, particularly in females ($P = 0.009$). Myocardial diastolic and overall function at rest was enhanced in HC versus EA ($P < 0.001$). During exercise, heart volumes and output per unit of body size did not differ between ethnicities, whereas larger heart volumes per unit of LBM were found in HC versus EA in females ($P \leq 0.003$). At high exercise intensities, VO_2 (−16%) and the arteriovenous O_2 difference (−28%) were markedly reduced in HC compared with EA in females ($P \leq 0.024$). In males, no physiological difference between HC and EA was observed during exercise.

Interpretation Notwithstanding lower LBM, HC are characterised by similar BV and cardiac capacity but reduced peak VO_2 than EA in females, partly explained by low ethnic-specific blood O_2 carrying capacity.

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Keywords: Hans Chinese; Sex dimorphism; Body composition; Regional adiposity; Lean body mass; Circulating haemoglobin mass; Blood volume; Cardiorespiratory fitness

Introduction

Approximately 20% of the human population can be classified as Han Chinese (HC), the world's largest ethnic group, currently surpassing 1.3 billion individuals.[1] Based on genetic analyses of ancient human remains,[2] HC have predominantly inhabited the territories of the current People's Republic of China for at least the past 3 millennia. With the lowest relative share of migrant inflow of any country in the world recorded by China since these data have been analysed (1990),[3] HC represents a highly uniform ethnic group at present and plausibly for the following decades. Academic attention is increasingly being directed towards distinctive socio-cultural characteristics of HC.[4] In contrast, relatively little is known regarding their potentially unique physiology. Notably, the function of the cardiorespiratory system, including prominent prognostic factors,[5,6] has yet to be directly assessed in

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Research in context

Evidence before this study

Little is known regarding the essential physiology of the Hans Chinese (HC) ethnicity. Namely, the function of the cardiorespiratory system, including strong prognostic factors of mortality, remained to be directly assessed in HC and contrasted with established values in other ethnicities. Thus far, the vast majority of human studies underpinning contemporary medical knowledge on the respiratory capacity to consume O_2 (VO_{2peak}) and cardiac capacity to pump blood (Q_{peak}) have included individuals from the European-American (EA) ethnicity.

Added value of this study

This study originally revealed ethnic disparities concerning the main determinants of cardiorespiratory fitness in HC, as contrasted with the prevailing ethnic specimen in the scientific literature (EA). HC and EA were closely matched by constitutional factors such as age, sex, health status and the principal potential confounding factor, i.e., physical activity (specifically involving aerobic exercise stimuli targeting the cardiovascular system). Marked ethnic differences were observed in females. HC females were characterised by lower blood O_2 carrying capacity, which was not compensated by enhanced cardiac function and Q_{peak} per unit of lean body mass during exercise, contributing to curtailed O_2 delivery, extraction and VO_{2peak} compared with EA females. No substantial ethnic difference in aerobic and cardiac capacities was detected in males.

Implications of all the available evidence

Considering the marked dissociation between the ethnic differences in Q_{peak} and VO_{2peak}, the prognostic value of VO_{2peak}, one of the strongest predictors of cardiovascular health and all-cause mortality, may need to be reappraised in the female HC population. Furthermore, future studies are warranted to establish whether low haemoglobin concentration is an intrinsic biological trait of HC females, entailing a chronic limitation to deliver and thereby consume O_2 per unit of blood flow.

HC and contrasted with established values in other ethnicities.

Sound knowledge on the respiratory capacity to consume O_2 (VO_{2peak}) and cardiac capacity to pump blood (Q_{peak}) as well as its main physiological determinants/correlates is available in Caucasian individuals, more specifically belonging to the European-American (EA) ethnic group—referring to European or American individuals with all known relatives from European ancestry.[7–9] In fact, the vast majority of human studies underpinning contemporary medical knowledge have included EA as participants.[10] To date, the parallelism between the cardiorespiratory system in HC and EA ethnicities has merely been indirectly.[11] In a large population study comprising 964 healthy HC throughout the adult lifespan, absolute VO_{2peak} (O_2 consumed per unit of time) was ~40% lower than predicted values according to equations based on EA populations.[11] Such a remarkable quantitative gap between HC and EA is unlikely to be exclusively explained by well-known differences body size and weight.[12] As a primary causative factor, large ethnic divergences in physical activity between HC and EA could be the main explanation for those in VO_{2peak} and its underlying physiological determinants.[13] In addition, body composition, with HC prevalently (and plausibly inherently) presenting higher body fat and lower lean body mass (LBM) per unit of body size than EA,[14] may partly contribute to limit VO_{2peak} in HC.[15,16] Moreover, arterial stiffness, a strong correlate of body composition and VO_{2peak}, seems to be remarkably elevated in HC.[17] Furthermore, potentially reduced blood volume (BV) might restrict cardiac filling and output (Q) via the Frank-Starling mechanism ('Law of the heart'), resulting in decreased systemic O_2 delivery exacerbated by low blood O_2 carrying capacity in HC relative to EA.[7,18–22]

The question arises whether HC and EA presenting with similar constitutional factors such as age, sex, health status and precisely matched by the principal potential confounding factor, i.e., physical activity (specifically involving aerobic exercise stimuli targeting the cardiovascular system), would present distinct aerobic and cardiac capacities per unit of body size, weight, or LBM. In such instance, HC would be physiologically distinct, and consequently, the prognostic value provided by the strongest determinants of cardiovascular health and all-cause mortality (VO_{2peak} and Q_{peak}, as established in EA) would plausibly need to be revised in an ethnic-specific manner for HC.[5,6,23] Accordingly, the purpose of the present study was to elucidate whether aerobic and cardiac capacities, as well as their primary determinants are inherently different in healthy HC compared with EA matched by major constitutional and confounding factors. We hypothesised a generalised reduction of VO_{2peak}, Q_{peak} and BV per unit of body size or weight in HC versus EA, an ethnic gap that would vanish if aerobic and cardiac capacities are normalised by LBM, i.e., the essential difference in body composition.[15,16]

Methods

Study participants

A total of 140 HC and EA healthy adult individuals were recruited in the cities of Hong Kong (China) and Calgary (Canada), respectively, via equivalent online and

printed advertisements in English and Traditional Chinese. HC (n = 70; 24–78 yr) and EA (n = 70; 21–77 yr) were matched by age, sex and physical activity (total and aerobic exercise-specific duration and average intensity). All participants had to present definite self-identified ethnicity (EA or HC) supported by legal name, country of birth, residential history as well as the absence of any known ancestor of distinct ethnicity. The self-identified ethnicity method demonstrates a very high percentage of agreement (>90%) with genetic-based measures of ancestry specific to HC and EA.[24,25] A few individuals (n = 4) belonging to mixed-ethnic backgrounds were not included in the study. Exercise training history and moderate-to-vigorous physical activity (MVPA, total and specific to aerobic (also known as endurance) exercise) over participant's lifetime as well as during the last 3 months prior to the study, the latter comprising a detailed description of physical activities additionally including the average ratio of perceived exertion (RPE), were assessed at screening, as previously described.[26]

Inclusion criteria comprised healthy status according to health/clinical questionnaires and resting echocardiography/ECG screening, absence of current medical symptoms and medication limiting incremental exercise testing, and no history of cardiac, pulmonary, haematological and/or neuromuscular conditions or diseases. The exclusion criteria comprised a lifetime history of extreme exercise training (MVPA >10 h*wk^{-1} for ≥2 yr) to preclude the potential presence of chronic cardiac adaptations dissociated from recent (past 3 months) physical activity stimuli. The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority West Cluster (UW 21-401)/ Conjoint Health Research Ethics Board (REB18-1654) of the University of Calgary and conducted in accordance with the declaration of Helsinki. Prior to the start of the experiments, informed oral and written consents were obtained from the participants.

Experimental design

All participants (HC and EA) followed a uniform study protocol (prior to testing) according to health and clinical questionnaires. They were instructed to avoid vigorous exercise, alcohol and caffeine 24 h prior to testing, as well as to maintain their usual baseline activity and daily dietary habits throughout the study. All measurements were performed in a single visit to the laboratory after a fasting period (≥4 h) to prevent confounding postprandial hemodynamic alterations.[27] The average time of day at which the measurements were performed was matched between EA and HC by scheduling prospective participants in EA or HC groups according to the average time of previous participants in the opposite group along with covariate adaptive randomisation, including age (<45/≥45 yr), sex (female/male) and physical activity (<5/≥5 h of MVPA-endurance), to ensure that these variables were matched between groups According to previous studies, the specific day of the menstrual phase was noted (if applicable) but not fixed for the day of testing as it does not influence the study outcomes.[28–30] Prior to testing, the participants completed health and clinical questionnaires in English and/or Chinese and rested in supine position for 20 min in order to stabilise cardiovascular, hemodynamic and haematological variables. These questionnaires, in addition to the aforementioned self-identified data, covered disease history (including family history of disease), physical activity history, diet/supplement history (if the participant reported any type of food restriction, e.g., with vegetarian diets), female-specific (e.g., menstrual-related) health information, blood donation history (if any), as well as detailed information regarding physical activity, food, supplement, medication (if any) and fluid intake over the last 24 h. Resting measurements were performed on the horizontal (supine) platform that contained the exercise testing equipment, with the legs straight and relaxed, and the feet not attached to the cycle ergometer (KICKR Core, Wahoo, USA). The ergometer was integrated inside a self-manufactured lower body pressure (LBP) chamber allowing moderate left-lateral tilting (set to 17° relative to the horizontal) to facilitate precise cardiac imaging from rest until peak exercise as established in previous studies.[7,15,16,31,32] The ambient pressure inside the LBP during exercise is fixed to −50 mm Hg to elicit the hemodynamic load characteristic of the upright position,[33] which is a physiological requirement to achieve peak heart rate (HR_{peak}) and VO_{2peak} in humans.[7,34,35] In this respect, supine cycling exercise with an LBP of −50 mm Hg is considered a model of upright exercise with regard to the central and peripheral (skeletal muscle) circulation.[34]

Measurements

Body composition

Body composition was assessed via dual-energy x-ray absorptiometry (DXA) (Hologic QDR 4500; Hologic, Inc, Bedford, USA).[36] The participants were instructed to sit down in the middle of the scanning table and lay supine with their spine aligned with the marked longitudinal midline. Once they were in the supine position, their arms were positioned along their side with the palms pronated, to standardise the scanned area. A small (~5 cm) gap was maintained between upper limbs and trunk and between legs to facilitate segmentation for regional assessments. Total LBM, fat body mass and bone mineral content were determined. All scans were performed by the same operator, with a within-subject coefficient of variation of 1.8 and 2.0% for total and lower body LBM, and 2.0 and 2.9% for total and lower body fat percentage, respectively.

Cardiac structure, function and hemodynamics

Apical four-chamber and two-chamber cine-loops were recorded via high-resolution ultrasound (Mindray Medical M9, USA) at rest, during predetermined levels of

incremental exercise relative to peak heart rate (HR_{peak}) (60, 70, 80, 90 and 100% HR_{peak}, hence comprising multiple measurements at the plateau phase of cardiac filling)[7,37] in a cycle ergometer designed to facilitate maximal effort and accurate echocardiography (described in the 'Experimental design' subsection).[7,16] Following the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations, cardiac chamber quantification including left ventricular end-diastolic and end-systolic volumes (LVEDV, LVESV) was performed offline using the modified Simpson method (biplane method of disks) by tracing the endocardial border of the left ventricle (LV) in apical four-chamber and two-chamber views at end-diastole and end-systole.[38,39] Stroke volume (SV) was determined by the difference between LVEDV and LVESV. The product of SV and HR provided Q. Right (RA) and left atrial (LA) volumes were determined via the single plane Simpson's method of disks from the apical four-chamber view at end-systole, according to current recommendations.[38–40] Right ventricular dimensions were not analysed due to the uncertain imaging quality of such a morphologically complex chamber.[41] The within-subject coefficient of variation of key echocardiographic measurements during incremental exercise in our laboratory is ≤5% for LV volumes and ≤7% for atrial (RA, LA) volumes. Cardiac volumetric variables are typically normalised by body surface area (BSA = 0.007184*weight$^{0.425}$*height$^{0.725}$) to mitigate the confounding impact of body size and thus they were primarily presented.[42] Regarding the assessment of LV diastolic function, transmitral inflow velocities were determined by pulsed-wave Doppler with the sample volume placed between the mitral leaflet tips in the apical four-chamber view. The peak inflow velocities during early (E) and late (A) diastole were measured and the E/A velocity ratio was calculated. The assessment of diastolic function also included myocardial tissue e' and a' velocities measured via tissue Doppler imaging (TDI) in left lateral and septal ventricular walls adjacent to the mitral annulus. The ratio of E and septal e' (E/e') was determined according to established guidelines.[38,39] The following time intervals were measured from TDI recordings in the septal ventricular wall: ejection time (ET), filling time (FT), isovolumic relaxation time (IVRT) and isovolumic contraction time (IVCT). The myocardial performance index (MPI), a global marker of LV diastolic and systolic function, was calculated as (IVRT + IVCT)/ET.[43] The assessment of diastolic function was performed at rest due to the overlap of E and A mitral waves with moderate exercise intensity. All echocardiographic measurements were performed in duplicate.

Blood pressure, comprising systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP), was assessed at rest in the upper arm via the gold standard auscultatory method using a mercury sphygmomanometer. The same method was successfully implemented to measure blood pressure during exercise in a subset of HC (n = 38) and EA (n = 59) matched by age (59.6 ± 10.7 vs. 58.2 ± 13.9 yr, P = 0.618), sex (47 vs. 46% females, P = 1.000) and physical activity (total MVPA: 6.4 ± 3.9 vs. 5.7 ± 2.9 h*wk^{-1}, P = 0.356; MVPA-endurance: 5.7 ± 3.9 vs. 5.2 ± 3.1 h*wk^{-1}, P = 0.525; RPE-endurance: 11.9 ± 2.5 vs. 11.6 ± 2.6, P = 0.527). Blood pressure measurements during exercise were performed at a fixed relative intensity (anaerobic threshold) as determined by the point at which respiratory exchange ratio (RER) reached 0.85 during the incremental exercise test, as described in the following subsection.[44] Total peripheral resistance (TPR) was calculated as the ratio of MAP and Q.[16]

Aerobic capacity and arteriovenous O_2 difference (a-vO_2 diff)

O_2 uptake (VO_2) and CO_2 output were continuously measured throughout an established incremental exercise protocol using a mixing chamber system (CardioCoach VO_2, KORR Medical, USA), as previously described.[7,15,29,31,32] Following a warm-up period at 10–30 W, the workload was progressively increased by 10–30 W increments every 50 s until exhaustion was reached in the recommended total duration of 7–10 min.[45] Calibration of the gas analysers and the flowmeter was performed prior to each test. Values were averaged over 15 s.[46] The highest average value defined peak O_2 uptake (VO_{2peak}) provided that at least two of the following established criteria were fulfilled: plateau in O_2 uptake despite increased workload, age- and body position-predicted HR_{peak} +/− 10 bpm[35,47] and/or RER > 1.[48] The arterio-venous O_2 difference (a-vO_2 diff) was calculated according to the Fick principle (VO_2 = Q × a-vO_2 diff) at each exercise intensity (60, 70, 80, 90 and 100% HR_{peak}).

Haemoglobin mass (Hb_{mass}) and intravascular volumes

Total circulating Hb_{mass} and intravascular volumes, including BV, total red blood cell volume (RBCV) and plasma volume (PV), were determined using the classic carbon monoxide (CO) rebreathing technique integrated in a semi-automated system with a very low typical error of measurement (TE ≤ 1.2%), as previously detailed.[7,49] In brief, 2 mL of blood were sampled at rest (before the exercise test) from the participant's median cubital vein via a 20-G venflon (BD, USA) and analysed immediately in duplicate for resting percent carboxyhemoglobin (%HbCO), haemoglobin (Hb) concentration and hematocrit (Hct) (ABL80, Radiometer, Denmark). These blood gas analyses were repeated in a blood sample (2 mL) taken immediately after exercise termination. Following the recovery period (20 min) after the exercise test, the participants breathed 100% O_2 plus a bolus of 1.5 mL/kg of 99.5% chemically pure CO (CO H.P. Grade, SG, Hong Kong) in a closed breathing circuit for 10 min in order to determine Hb_{mass}, which is not affected by acute exercise.[50] An additional 2 mL

blood sample was obtained exactly after 10 min of CO-rebreathing and analysed in duplicate, as aforementioned. The change in %HbCO induced by CO administration is used to calculate Hb_{mass} conforming to the dilution principle, taking into account the small amount of CO that remains in the rebreathing circuit at the end of the procedure.[7,49] Hb_{mass} along with resting Hb concentration and Hct comprised the required variables to determine resting intravascular volumes (BV, RBCV, PV).[7,49]

Statistical analysis

All statistical analyses were performed with SPSS 26.0 (SPSS, USA). Data were tested for normal distribution with the Kolmogorov–Smirnov test and for homogeneity of variances with the Levene's test. Ethnic differences in Q_{peak} and VO_{2peak} were the main primary outcomes. According to a power analysis of previous findings,[7,28,29] a sample size of 30 participants per group provided ≥90% power to detect ≥50% of the expected ethnic difference in VO_{2peak} and Q_{peak} with a two-sided α of 5%.[11] Two-way ANOVA with repeated measures was performed to assess pulmonary gas exchange and cardiac variables during incremental exercise, with ethnicity (HC, EA) and exercise intensity (60, 70, 80, 90 and 100% HR_{peak}) as between- and within-subject factors, respectively, along with their interaction. Post-hoc comparisons at each exercise intensity were conducted provided that F was significant in the ANOVA. Planned ethnic comparisons of peak pulmonary gas exchange and cardiac variables and their relationship with haematological variables were assessed via the independent *t*-test. Likewise, ethnic comparisons at rest were determined via the independent sample *t* test and the Fisher's exact test for continuous and categorical variables, respectively. The Cohen's *d* coefficient was calculated as a measure of the effect size of ethnic differences in main outcomes and its physiological determinants. Finally, the influence of confounding factors (age, sex, physical activity) on main results was assessed via ANCOVA. All data were reported as mean ± SD unless otherwise stated. A two-tailed *P*-value less than 0.05 was considered significant.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, interpretation and writing of the manuscript.

Results

General characteristics

Table 1 presents demographic, anthropometric, body composition, cardiac and hemodynamic variables at rest. Age, sex and physical activity (total MVPA, MVPA-endurance and RPE-endurance) were closely matched between HC and EA ($P \geq 0.578$). The type of endurance exercise predominantly comprised (≥95%) lower body physical activities such as running and/or cycling in all subgroups (HC-female/male, EA-female/male). All individuals were non-smokers and non-obese (body mass index (BMI) < 30 $kg*m^{-2}$). The majority of females had reached menopause, with a similar prevalence in both ethnicities (HC: 21/30, EA: 25/30; $P = 0.360$). HC demonstrated lower anthropometric indices (height, weight, BSA), higher body fat percentage and lower LBM percentage than EA irrespective of sex ($P \leq 0.014$).

With respect to resting cardiac structure, ethnic differences were observed in females. LV volumes (LVEDV and SV) were smaller (normalised by BSA) in HC versus EA in females ($P \leq 0.049$). As for resting cardiac function, HC, irrespective of sex, exhibited a generalised enhancement of diastolic function, evidenced by lower septal E/e' ratio and IVRT compared with HC ($P < 0.001$). Specifically in females, HC additionally presented improved systolic function, with shortened IVCT and longer tricuspid S′ compared with EA ($P \leq 0.005$). Overall, MPI was largely reduced in HC versus EA irrespective of sex ($P < 0.001$), denoting a superior resting myocardial function in HC.

Blood O_2 carrying capacity and intravascular volumes

Total circulating Hb_{mass}, Hb concentration and intravascular volumes at rest are presented in Table 2. HC and EA showed similar Hb_{mass} per kg of body weight, with females presenting lower values than males irrespective of ethnicity ($P < 0.001$). Blood O_2 carrying capacity, as defined by Hb concentration, was lower in HC compared with EA in females ($P = 0.009$, $d = 0.688$) but not in males ($P = 0.060$), independently of differences in PV at rest. Immediately after exercise, Hb concentration was decreased in HC relative to EA in females (13.1 ± 1.1 vs. 14.3 ± 0.8 $g*dL^{-1}$, $P < 0.001$, $d = 1.245$) and males (15.1 ± 1.2 vs. 16.0 ± 1.1 $g*dL^{-1}$, $P = 0.002$, $d = 0.782$), plausibly due to the established (although not directly measured in this study) decreasing effect of exercise on PV.[51] As for the intravascular volumes at rest, PV was augmented and RBCV reduced per kg of body weight in HC versus EA irrespective of sex ($P \leq 0.040$).

Cardiac structure, function and hemodynamics from moderate to peak exercise

Fig. 1 displays heart volumes (normalised by BSA), HR and Q in response to gradually increasing exercise intensity. Overall, no ethnic difference was present in RA, LA, LVEDV, SV, HR and Q during incremental exercise ($P \geq 0.288$). Nonetheless, interactions between ethnicity and exercise intensity were present for LVEDV, SV and Q in females ($P \leq 0.038$). Post-hoc and planned comparisons revealed increased LVEDV and SV at peak exercise ($LVEDV_{peak}$, SV_{peak}) in HC versus EA in females ($P \leq 0.047$, $d \geq 0.444$) but not in males ($P \geq 0.719$). When heart volumes were normalised by LBM, larger RA, LVEDV, SV and Q during incremental exercise were

	EA			HC		
	♀	♂	All	♀	♂	All
n	30	40	70	30	40	70
Age (yrs)	58.8 ± 11.3	57.2 ± 14.9	57.9 ± 13.9	57.1 ± 12.8	52.9 ± 14.3	54.7 ± 13.8
Height (cm)	163.2 ± 7.1	177.7 ± 6.8[b]	171.5 ± 10.0	158.9 ± 6.1[a]	170.0 ± 6.3[a,b]	165.8 ± 8.6[a]
Weight (kg)	60.8 ± 8.7	78.9 ± 10.0[b]	71.1 ± 13.0	54.0 ± 7.5[a]	67.2 ± 8.5[a,b]	61.8 ± 10.4[a]
BSA (m^2)	1.65 ± 0.13	1.96 ± 0.14[b]	1.83 ± 0.21	1.54 ± 0.12[a]	1.78 ± 0.12[a,b]	1.68 ± 0.17[a]
MVPA ($hr*wk^{-1}$)	5.3 ± 2.6	6.3 ± 3.2	5.9 ± 3.0	5.4 ± 3.1	6.5 ± 4.8	6.0 ± 4.2
MVPA-endurance ($hr*wk^{-1}$)	5.0 ± 2.7	5.9 ± 3.4	5.5 ± 3.1	5.1 ± 3.1	5.7 ± 4.3	5.4 ± 3.8
RPE-endurance exercise	11.0 ± 3.2	12.2 ± 2.4	11.6 ± 2.8	11.1 ± 3.2	12.5 ± 2.6	11.9 ± 2.9
Body composition						
LBM (kg)	42.4 ± 5.0	61.4 ± 6.4[b]	53.3 ± 11.1	36.0 ± 4.7[a]	51.3 ± 5.7[a,b]	44.7 ± 9.3[a]
Fat (kg)	16.4 ± 5.2	14.9 ± 5.0	15.6 ± 5.1	17.6 ± 4.4	15.1 ± 4.6[b]	16.2 ± 4.7
Fat percentage (%)	26.6 ± 5.3	18.6 ± 4.5[b]	22.0 ± 6.3	31.5 ± 5.2[a]	21.6 ± 4.6[a,b]	25.8 ± 6.9[a]
Cardiovascular structure and function						
RA ($mL*m^{-2}$)	15.0 ± 4.7	16.6 ± 5.0	15.9 ± 4.9	14.2 ± 5.9	15.9 ± 4.5	15.2 ± 5.1
LA ($mL*m^{-2}$)	20.1 ± 9.1	19.2 ± 6.8	19.6 ± 7.8	16.7 ± 6.0	17.2 ± 4.9	17.0 ± 5.4[a]
LVEDV ($mL*m^{-2}$)	70.0 ± 12.9	78.2 ± 19.5[b]	74.7 ± 17.4	63.6 ± 11.7[a]	75.4 ± 15.3[b]	70.3 ± 15.0
LVESV ($mL*m^{-2}$)	11.0 ± 3.7	12.1 ± 4.8	11.6 ± 4.3	9.9 ± 2.8	12.8 ± 4.7[b]	11.6 ± 4.3
LV_{mass} ($g*m^{-2}$)	74.3 ± 15.6	82.1 ± 16.1	78.7 ± 16.2	65.6 ± 18.3	76.7 ± 17.2[b]	71.8 ± 18.4[a]
SV ($mL*m^{-2}$)	60.0 ± 12.1	67.7 ± 16.5[b]	64.4 ± 15.2	53.8 ± 10.1[a]	62.6 ± 12.1[b]	58.8 ± 12.0[a]
HR (bpm)	58.3 ± 7.3	55.0 ± 5.8[b]	56.4 ± 6.7	62.8 ± 7.9[a]	61.5 ± 10.4[a]	62.0 ± 9.4[a]
Q ($L*min^{-1}*m^{-2}$)	3.6 ± 1.3	3.7 ± 0.9	3.7 ± 1.1	3.3 ± 0.5	3.8 ± 0.8[b]	3.6 ± 0.7
MAP (mm Hg)	95.3 ± 17.4	96.6 ± 11.3	96.0 ± 14.1	93.8 ± 9.0	96.7 ± 10.4	95.4 ± 9.8
TPR ($dyn*s*cm^{-5}$)	1364 ± 429	1132 ± 290[b]	1229 ± 371	1504 ± 258	1186 ± 279[b]	1331 ± 312
Tricuspid S′ ($cm*s^{-1}$)	11.4 ± 1.8	11.5 ± 1.7	11.5 ± 1.7	12.9 ± 2.0[a]	12.2 ± 1.8	12.5 ± 1.9[a]
Mitral E/A ratio	1.06 ± 0.25	1.09 ± 0.36	1.07 ± 0.31	1.17 ± 0.38[a]	1.35 ± 0.40[a]	1.27 ± 0.40[a]
Septal E/e′ ratio	6.5 ± 1.7	5.9 ± 1.4	6.2 ± 1.6	4.8 ± 1.0[a]	5.0 ± 1.0[a]	4.9 ± 1.0[a]
Septal IVRT (ms)	69.0 ± 13.8	75.2 ± 18.3	72.4 ± 16.6	55.8 ± 14.6[a]	60.2 ± 13.8[a]	58.3 ± 14.2[a]
Septal IVCT (ms)	65.0 ± 11.2	60.0 ± 11.2	62.3 ± 11.4	54.7 ± 11.4[a]	54.5 ± 14.0	54.6 ± 12.8[a]
Septal MPI	0.39 ± 0.06	0.40 ± 0.08	0.40 ± 0.07	0.31 ± 0.87[a]	0.32 ± 0.10[a]	0.32 ± 0.10[a]

Data are expressed as mean ± SD. BSA, body surface area; EA, European-American; HC, Hans Chinese; HR, heart rate; LA, left atrial volume; LBM, lean body mass; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LV_{mass}, left ventricular mass; MAP, mean arterial pressure; Mitral E/A ratio, ratio of peak blood flow velocity in early diastole (E wave) to peak blood flow velocity in late diastole due to atrial contraction (A wave); MPI, myocardial performance index; MVPA, moderate-to-vigorous physical activity; MVPA-endurance, moderate-to-vigorous physical activity comprising aerobic (endurance) exercise; RA, right atrial volume; RPE-endurance exercise, ratio of perceived exertion of endurance exercise; Septal E/e′ ratio, ratio of peak blood flow velocity to tissue myocardial velocity in early diastole in the septum of the heart; Septal IVCT, isovolumic contraction time in the septum of the heart; Septal IVRT, isovolumic relaxation time in the septum of the heart; SV, stroke volume; Tricuspid S′, peak lateral tricuspid annular systolic velocity; TPR, total peripheral resistance. [a]$P < 0.05$, HC compared with EA (including all individuals, females or males). [b]$P < 0.05$, ♂ compared with ♀ within each ethnicity.

Table 1: **General characteristics of study subjects at rest.**

predominantly observed in HC compared with EA in females ($P \leq 0.003$, $d \geq 0.993$) (Supplemental Figure S1). At a fixed relative exercise intensity (anaerobic threshold), MAP was lower in HC versus EA in females (132.8 ± 8.8 vs. 150.3 ± 31.0 mm Hg, $P = 0.009$), but not in males (136.2 ± 12.9 vs. 141.7 ± 27.9 $dyn*s*cm^{-5}$, $P = 0.410$), while TPR did not differ between ethnicities irrespective of sex (870.2 ± 201.0 vs. 996.0 ± 423.2 $dyn*s*cm^{-5}$, $P = 0.090$).

Oxygen uptake (VO_2) and arteriovenous oxygen difference (a-vO_2 diff) from moderate to peak exercise

The gradual increase in VO_2 per kg of body weight and a-vO_2 diff with higher exercise intensity is illustrated in Figs. 2 and 3, respectively. VO_2 throughout the incremental exercise test did not differ between HC and EA irrespective of sex ($P \geq 0.208$). Interactions between ethnicity and exercise intensity were detected in VO_2 in females ($P < 0.001$). Post-hoc and planned comparisons evidenced lower VO_2 in HC compared with EA in females at the two highest exercise intensities (90 and 100% HR_{peak}) ($P \leq 0.024$, $d \geq 0.773$). Similar results were observed for VO_2 normalised by LBM (Supplemental Figure S2). Likewise, a-vO_2 diff was lower in HC versus EA in females ($P = 0.020$), notably at 90 and 100% HR_{peak} ($P \leq 0.004$, $d \geq 1.374$) (Fig. 3). VO_2 was thus curtailed by reduced a-vO_2 diff in HC females as comprehensively presented in Fig. 4 conforming to the Fick principle.

	EA			HC		
	♀	♂	All	♀	♂	All
Hb_{mass} (g)	613 ± 79	939 ± 112[b]	799 ± 190	539 ± 137[a]	828 ± 121[a,b]	705 ± 192[a]
Hb_{mass} ($g*kg^{-1}$)	10.2 ± 1.3	12.0 ± 1.4[b]	11.2 ± 1.6	10.0 ± 2.2	12.3 ± 1.7[b]	11.3 ± 2.2
Hb ($g*dL^{-1}$)	13.3 ± 0.6	14.9 ± 1.0[b]	14.2 ± 1.2	12.8 ± 0.8[a]	14.5 ± 1.1[b]	13.8 ± 1.3[a]
Hct (%)	40.7 ± 1.9	45.8 ± 3.0[b]	43.6 ± 3.6	39.2 ± 2.5[a]	44.4 ± 3.5[b]	42.0 ± 4.2[a]
RBCV (mL)	2070 ± 268	3133 ± 382[b]	2677 ± 627	1657 ± 423[a]	2539 ± 371[a,b]	2161 ± 589[a]
PV (mL)	3015 ± 406	3777 ± 509[b]	3450 ± 600	2972 ± 608	3759 ± 606[b]	3451 ± 600
BV (mL)	5085 ± 645	6910 ± 753[b]	6128 ± 1150	4628 ± 1009[a]	6298 ± 890[a,b]	5583 ± 1252[a]
RBCV ($mL*kg^{-1}$)	34.4 ± 4.4	40.0 ± 4.5[b]	37.6 ± 5.2	30.6 ± 6.7[a]	37.7 ± 5.2[a,b]	34.7 ± 6.8[a]
PV ($mL*kg^{-1}$)	50.0 ± 6.1	48.4 ± 7.4	49.1 ± 6.9	55.1 ± 10.9[a]	55.9 ± 8.8[a]	55.6 ± 9.7[a]
BV ($mL*kg^{-1}$)	84.3 ± 9.9	88.3 ± 10.4	86.7 ± 10.3	85.7 ± 17.0	93.6 ± 12.6[a,b]	90.2 ± 15.1

Data are expressed as mean ± SD. BV, blood volume; EA, European-American; Hb, haemoglobin concentration; Hb_{mass}, haemoglobin mass; HC, Hans Chinese; Hct, hematocrit; PV, plasma volume; RBCV, red blood cell volume. [a]$P < 0.05$, HC compared with EA (including all individuals, females or males). [b]$P < 0.05$, ♂ compared with ♀ within each ethnicity.

Table 2: **Blood attributes: total circulating haemoglobin mass (Hb_{mass}) and intravascular volumes at rest.**

Fundamental ratios

The relationship between inherently coupled pulmonary, cardiac and haematological variables according to established physiological principles is illustrated in Supplemental Figure S3. All ratios comprising VO_{2peak} and a haematological (BV, Hb_{mass}) or peak cardiac ($LVEDV_{peak}$, SV_{peak}, Q_{peak}) variables were lower in HC relative to EA in females ($P \leq 0.024$). In contrast, the ratio between $LVEDV_{peak}$ and BV was higher in HC compared to EA in females ($P = 0.019$). In males, no ethnic difference was observed in any ratio ($P \geq 0.483$).

Discussion

This study compared the essential physiology of aerobic and cardiac capacities of two major ethnic groups, HC and EA, matched by age, sex and physical activity. Considering sex-specific EA as the control group, the main findings are: 1) exercise heart volumes and output per unit of body size or LBM, as well as O_2 uptake and extraction are remarkably similar between ethnicities in males; 2) per unit of LBM, exercise heart volumes and output are prevalently enhanced in HC, notably in females; 3) blood O_2 carrying capacity is reduced in HC females; 4) VO_{2peak} is diminished in HC females, even when normalised by LBM, which is paralleled by a marked female-specific blunting of a-vO_2 diff at high exercise intensities.

Notwithstanding the mainstream pressures of our time, the existence of heritable markers denotative of certain ethnic groups is undeniable.[24,25] In fact, self-identified ethnicity among EA, East Asian, or African categories almost perfectly concur (99.9%) with machine-driven genetic cluster classifications.[25] The acceptance of such a biological reality does not necessarily entail the presence of physiologically relevant differences between ethnicities. Indeed, similar structure and function of vital organs in individuals with dissimilar genotype is the norm rather than the exception, an axiom that underpins the study of human and medical physiology using ample categorisations.[52,53] Yet, whether the impact of ethnic-related heritability on strong prognostic factors follows the norm or the exception has remained largely unexplored. Herein, we hypothesised the presence of substantial ethnic differences in cardiac capacity per unit of body size between HC and EA according to ethnic-specific body composition,[15,16] with HC typically presenting with reduced LBM,[14] which is primarily comprised of skeletal muscle,[54] the tissue explaining the largest share of the metabolic demand during exercise. Unexpectedly, Q from moderate to peak exercise (hence encompassing the crucial plateau phase of cardiac filling)[7,37] as well as its primary volumetric determinants, i.e., BV, LV filling (LVEDV) and SV, were not lower per unit of body weight or size in HC compared with EA (Table 2, Fig. 1). Moreover, when normalised by LBM, marked increases in LVEDV, SV and Q at peak exercise were detected in HC, specifically in females (Supplemental Figure S1). Accordingly, despite differences in body composition were confirmed between ethnicities (Table 1), HC did not demonstrate diminished cardiac capacity. These findings were accompanied by superior myocardial performance at rest, generally involving enhanced LV relaxation and contractile properties, in HC relative to EA, predominantly in females albeit also partially present in males. It is thus plausible that for the same age, sex and dose of endurance (aerobic) exercise, the HC heart exhibits further beneficial traits or adaptations, therefore being or becoming *fitter* to fulfil its main function, i.e., to meet metabolic needs via the delivery of blood with relatively low O_2 content, as developed in the following paragraph.

Coupled with Q, blood O_2 carrying capacity determines the ceiling of O_2 delivery to the systemic circulation. Importantly, it is the systemic delivery, not the

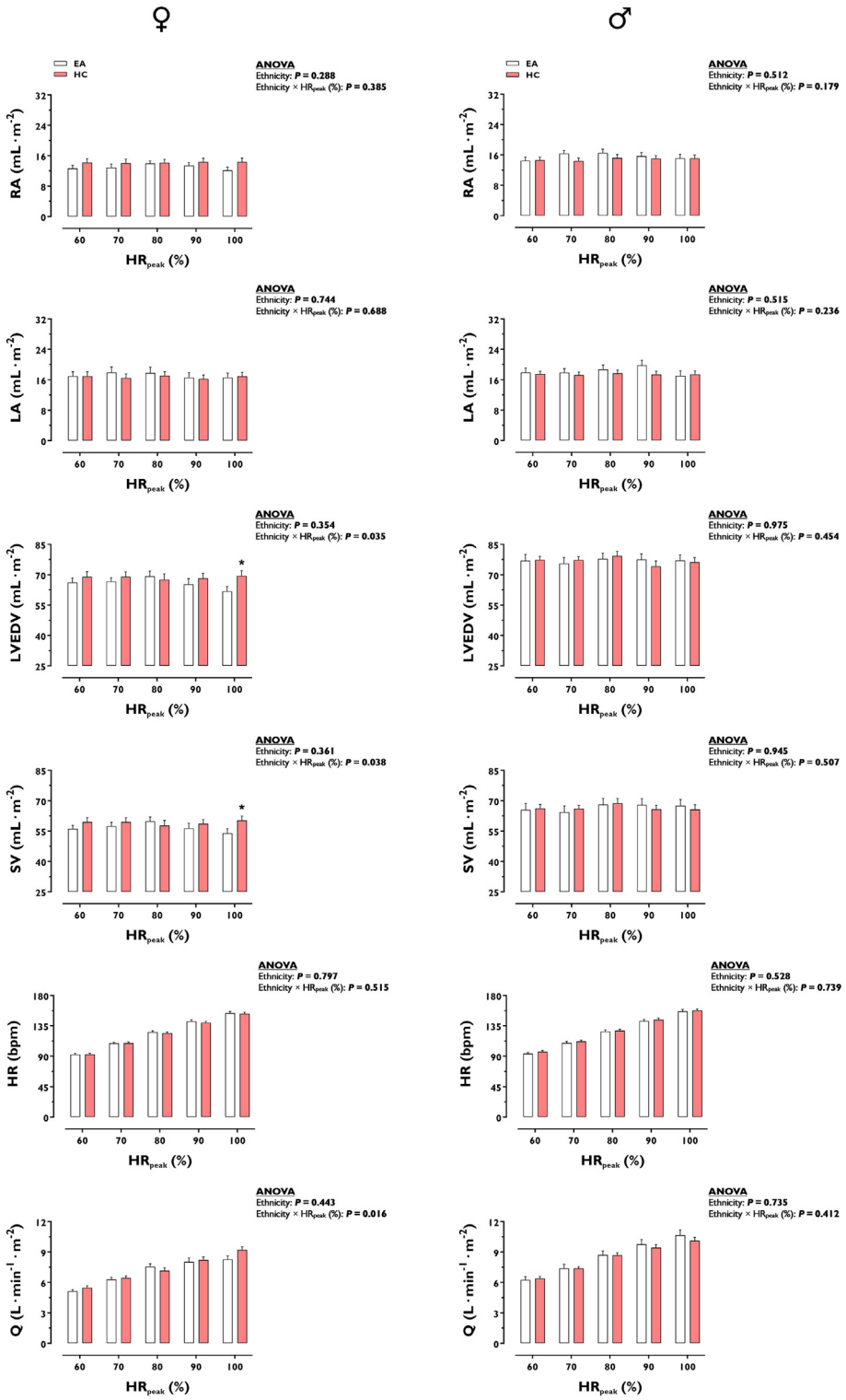

Fig. 1: **Heart volumes, rate and output during moderate to peak exercise in EA and HC according to sex**. Data are illustrated as mean ± SEM. *$P < 0.05$, HC compared with EA within each sex and exercise intensity. EA, European-American; HC, Hans Chinese; HR, heart rate; HR_{peak}, peak heart rate; LA, left atrial volume; LVEDV, left ventricular end-diastolic volume; Q, cardiac output; RA, right atrial volume; SV, stroke volume.

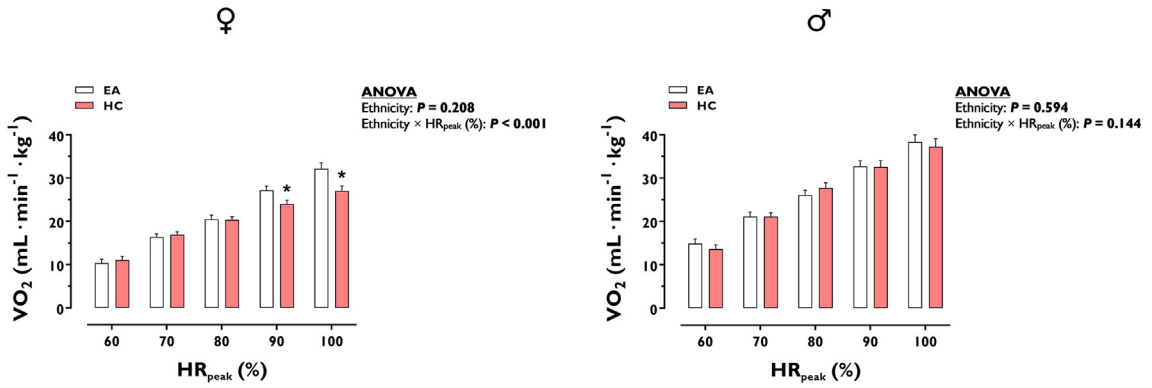

Fig. 2: **O_2 uptake (VO_2) during moderate to peak exercise in EA and HC according to sex**. Data are illustrated as mean ± SEM. *P < 0.05, HC compared with EA within each sex and exercise intensity. EA, European-American; HC, Hans Chinese; HR_{peak}, peak heart rate; VO_2, oxygen uptake.

potential extraction of O_2, what limits VO_2 during exercise, according to studies in EA.[31,53] Indeed, experimental reductions of the concentration of Hb able to carry O_2 results in proportional decrements in VO_2 at high exercise intensities (≥80% HR_{peak}) in healthy EA adult females and males.[32] This effect is mainly explained by the curtailment a-vO_2 diff.[32] In the present study, resting Hb concentration, i.e., the variable that defines blood O_2 carrying capacity, was lower (–0.5 g*dL^{-1}) in HC compared with EA in females (Table 2). Such a female-specific HC deficit in Hb concentration was magnified immediately after the exercise test (–1.2 g*dL^{-1}). The foreseen decrements in VO_2 and a-vO_2 diff in females were observed at the highest exercise intensities (90 and 100% HR_{peak}) (Figs. 2 and 3), precisely when the contribution of O_2 delivery to VO_2 becomes predominant.[55] In fact, considering the aforementioned difference in exercise Hb concentration (–1.2 g*dL^{-1}) and the known O_2-carrying capacity of 1 g of Hb (1.34 mL), the expected difference in a-vO_2 diff (–1.6 mL*dL^{-1}) concurs closely with the observed average difference during exercise in a-vO_2 diff (–1.4 mL*dL^{-1}) between HC and EA females (Fig. 3). It should be noted that in the present study (i) no participant had ever been diagnosed with anemia, (ii) diet abnormalities were not detected (according to health questionnaires fulfilled by the participants), and (iii) the sex-specific Hb concentration and the ethnic-related difference between HC and EA concurred with recently reported values in large population studies including these ethnicities (>60,000 individuals per ethnic group).[22] In this regard, low Hb concentration seems to be prevalent in HC populations, notably in women.[20,21] While subtle nutritional divergences may contribute to ethnic differences in Hb concentration in large population studies, these also demonstrate that HC and EA partly differ in the genetic basis of blood O_2 carrying capacity.[22] Therefore, it cannot be discarded

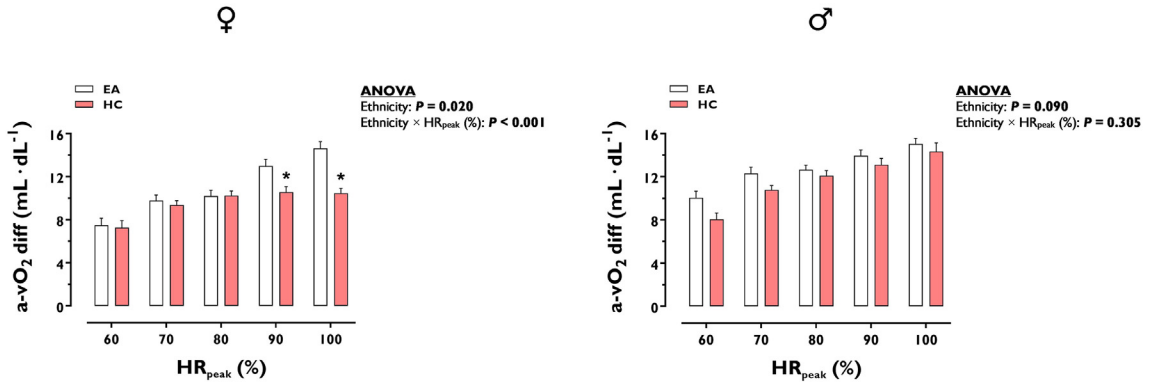

Fig. 3: **Arteriovenous O_2 difference (a-vO_2 diff) during moderate to peak exercise in EA and HC according to sex**. Data are illustrated as mean ± SEM. *P < 0.05, HC compared with EA within each sex and exercise intensity. EA, European-American; HC, Hans Chinese; HR_{peak}, peak heart rate.

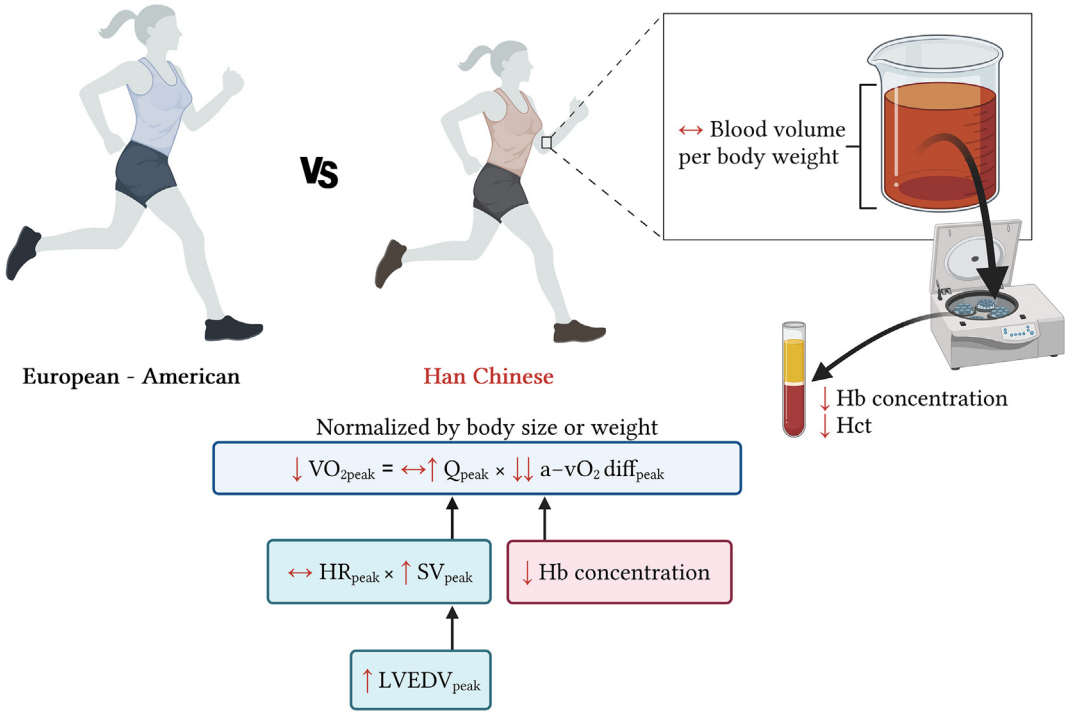

***Fig. 4:* Graphical synopsis of the physiological determinants of low aerobic capacity in HC females on the basis of the Fick principle**. The decrement in VO_{2peak} per unit of body size or weight (–16%) in HC relative to EA in females is explained by a marked decrement in a-vO_2 $diff_{peak}$ (–28%), which is not counterbalanced by enhanced Q_{peak} resulting from augmented cardiac filling ($LVEDV_{peak}$) and SV_{peak} in the former. Among the primary factors contributing to lower VO_{2peak}, reduced Hb concentration at peak exercise is expected to limit arterial O_2 content and thereby restrict a-vO_2 $diff_{peak}$ in HC females. a-vO_2diff_{peak}, peak arteriovenous O_2 difference; Hb, haemoglobin; Hct, hematocrit; HR_{peak}, peak heart rate; $LVEDV_{peak}$, left ventricular end-diastolic volume at peak effort (100% HR_{peak}); Q_{peak}, peak cardiac output; SV_{peak}, stroke volume at peak effort (100% HR_{peak}); VO_{2peak}, peak O_2 uptake.

that low Hb concentration is an inherent characteristic of HC females, entailing a permanent limitation to deliver and thereby consume O_2 per unit of blood flow to skeletal muscle (Fig. 4).[56] From the opposite perspective, for a given O_2 delivery to skeletal muscle, HC females must require additional blood flow and plausibly extra cardiac work to augment Q (unless blood flow distribution differs between ethnicities). *Extra* cardiac traits or adaptations might then be expected in HC females,[57,58] which take us back to the conclusion of the preceding paragraph.

A clear distinction has been made thus far with respect to the ethnic comparison in blood O_2 carrying capacity in females and males. However, the reality is not as neat as it could be inferred. While HC males did not present lower Hb concentration than EA males at rest ($P = 0.060$), a marked ethnic difference (–0.9 g*dL^{-1} in HC males vs. EA males) was observed immediately after the exercise test. In parallel, unlike the results obtained in females, cardiac and aerobic capacities were remarkably similar between ethnicities in males (Figs. 1–3). Therefore, a conceivable low Hb concentration and reduced arterial O_2 content at peak exercise were offset in HC males. Considering that systemic blood flow (Q) did not differ between HC and EA in males, either increased blood flow distribution towards active skeletal muscle and/or enhanced O_2 extraction via increased capillary density and/or myoglobin concentration in the former must be the counterbalancing factor(s).[59] Further experimental research will be required to elucidate the potential compensating peripheral mechanism in HC males.

The capacity to consume O_2 constitutes a prominent prognostic factor associated with cardiovascular and overall mortality in EA populations.[23] In fact, the assessment of VO_{2peak} has long been implemented in Western clinical settings as an objective quantitative criterion in the selection of candidates for heart transplantation.[5] The physiological and pragmatic foundation resides in the confidence that VO_{2peak} (a readily measurable variable) reflects cardiac capacity. VO_{2peak} is thus assumed to maintain a rather fixed quantitative relationship with Q_{peak} and its primary determinants.[53,60]

Herein, the fundamental ratios of VO_{2peak} with peak cardiac (Q_{peak}, $LVEDV_{peak}$, SV_{peak}) and haematological (BV, Hb_{mass}) determinants of cardiac and aerobic capacities were fairly constant in HC and EA in males (Supplemental Figure S3). In contrast, lower ratios were observed in HC relative to EA in females (Supplemental Figure S3). Therefore, VO_{2peak} in HC females is underlain by improved prognosis according to cardiac predictors of hard clinical outcomes[5,6] and haematological determinants of exercise capacity,[53] contrasted with EA matched by sex, age and physical activity. Consequently, the prognostic value of VO_{2peak} may need to be reappraised in an ethnic-specific manner in the female HC population. Furthermore, consideration should be given to the distribution of blood in the circulatory system at peak working capacity, as represented by the ratio of peak cardiac filling ($LVEDV_{peak}$) per BV.[28] This ratio was augmented in HC relative to EA in females (Supplemental Figure S3), which denotes an optimised BV distribution facilitating the Frank-Starling mechanism and thereby enhancing cardiac function. Whilst speculative, increased LV relaxation in HC females, as aforementioned according to resting measurements, could be a contributing factor explaining higher cardiac filling per unit of blood in this population. Using classic terminology from Guyton's model,[61] the female HC cardiovascular system may require lower mean systemic filling pressure to circulate blood, a valuable information with broad clinical applications.[61]

Limitations

Ethnic comparisons in human biology are expected to be prone to confounding, in part due to potential self-reporting bias in the description of ethnicity. Despite multiple efforts were implemented to control major constitutional and confounding factors, some subtle developmental and lifestyle differences between populations belonging to utterly distinct cultures may necessarily remain elusive to detection. It cannot thus be discarded that the herein ethnic differences could be partly attributed to a non-biological component. Moreover, the prognostic impact of the present ethnic differences remains to be assessed in future studies. Finally, it should be taken into account that current findings, based on non-invasive cardiac imaging, remain to be confirmed with invasive (catheterisation) methods, which are not influenced by the variability associated with the inherent limitations of cardiac imaging at the high temporal resolution required during exercise.

Conclusion

This study unveiled ethnic disparities concerning the main determinants of cardiorespiratory fitness in HC, as contrasted with the prevailing ethnic *specimen* underpinning contemporary knowledge in human physiology. Marked ethnic differences were observed in females. Notwithstanding a close match of age, sex and physical activity, HC females were characterised by lower blood O_2 carrying capacity, which was not compensated by enhanced cardiac function and Q per unit of LBM during exercise, contributing to curtailed O_2 delivery, extraction and aerobic capacity compared with EA. No substantial ethnic difference in aerobic and cardiac capacities was ascertained in males. Among the implications of this study, the prognostic value of VO_{2peak}, one of the strongest predictors of cardiovascular health and all-cause mortality, will plausibly need to be reappraised in the female HC population.

Contributors

DM designed the study. MG, CD and DM collected and analysed the data. DM drafted the manuscript. MG, CD, MYN, KHY and DM critically revised the manuscript and provided the final approval. DM and CD accessed and verified the data of this study and were responsible for the decision to submit the manuscript.

Data sharing statement

All data relevant to this study are presented in the manuscript and the supplementary material.

Editor note

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Declaration of interests

We declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100975.

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