Clarifying the Link Between the Blood Lactate Concentration and Cardiovascular Risk

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ABSTRACT

The blood lactate value at rest (Lac_{rest}) is linked to cardiovascular outcomes. It is unclear whether this association holds true in younger, healthy subjects, especially as the pathophysiological connection between Lac_{rest} and cardiometabolic disease is not well understood. The aim of this study is clarifying the link between Lac_{rest} and cardiovascular risk, and to study explanatory factors for the variance of Lac_{rest} concerning metabolism and physical activity in a population of healthy patient-athletes. The distribution and intra-individual variability of Lac_{rest} was assessed based on 9051 samples. The 10-year cardiovascular risk was then approximated using the Framingham risk score in a group of 1315 samples from patient-athletes. Cross-validated linear regression was used to analyze explanatory variables for Lac_{rest} and 10-year cardiovascular risk. Lac_{rest} is weakly associated with the Framingham score. This association disappears when adjusting for blood lipids. Lac_{rest} is also linked to the predominant type of exercise with endurance athletes featuring a higher Lac_{rest}. Lac_{rest} does not independently predict the estimated cardiovascular risk but is associated with lipid parameters. Moreover, the intra-individual variability of Lac_{rest} is high in a relevant number of subjects, which does not point towards the feasibility to use Lac_{rest} as an individual risk factor.

Introduction

Both exercise physiologists and clinicians have studied lactate metabolism for decades. Once assumed to be simply a byproduct of anaerobic energy metabolism, which might act as a substrate when conditions are aerobic, lactate actually is a signaling molecule with relation to metabolic regulation [1].

Clinically, blood lactate levels have been interpreted to point towards insufficient oxygen delivery (e. g., in sepsis or cardiac or bowel ischemia) [2–4] to tissues and other pathologies [5]. Moreover, blood lactate levels at rest (Lac_{rest}) and during exercise are also used as a marker of primary mitochondrial dysfunction and

hence, lack of oxidative capacity of the cells, due to hereditary enzyme defects [6] or even deconditioning [7].

Recent work based on data gathered during the Atherosclerosis Risk in Communities (ARIC) study has demonstrated an association between Lac_{rest} and cardiovascular outcomes [8], development of diabetes mellitus [9, 10], hypertension [11] und carotid atherosclerosis [12], which points towards a clinical significance of this parameter, possibly through its link to general energy metabolism.

As unfavorable metabolic changes manifesting at a very young age might already impact on long-term cardiovascular risk [13], the aim of this article, therefore, is to investigate the relationship between Lac_{rest} and cardiovascular risk with respect to blood lipids, physical fitness and in a relatively young study group of healthy patient-athletes.

Knowledge about both, the distribution of Lac_{rest} in a healthy population and its intraindividual variation in repeated measurements is an indispensable prerequisite to assess whether Lac_{rest} is suitable to point towards an increased cardiovascular risk on an individual level. To our knowledge, there is a scarcity of data concerning theses parameters. Therefore, and as a preliminary step for the key study aim, the distribution of the Lac_{rest} and the relation between inter- and intraindividual variation will be studied based on a large dataset of healthy patient-athletes.

Materials and Methods

The local hospitals ethics committee has approved the study. In a retrospective analysis of our database, 9051 datasets of 5575 individual patients ("patient-athletes", for subject characteristics, see ▶ **Table 1**) who visited our outpatient department in between 2007 and 2016 for lactate-based performance testing were identified that qualified to be further studied. The term "patient-athlete" is used because the subjects were either competitive or leisure-time athletes (from strength/speed or mainly endurance determined type of sports) or were performing the lactate-based performance test to establish regular physical activity (sedentary group). The subjects were allocated to their predominant type of physical adaptation by their self-reported primary sport during at least one year before the examination. This assignment was taken from the criteria in Olympic sports medicine [14]. These datasets were used to describe the distribution of Lac_{rest}.

For a subgroup of 836 of these subjects**,** replicate measurements of Lac_{rest} were available. This subgroup was analyzed to determine intra- to interindividual variation of Lac_{rest} (see below).

The key study sample consists of the 1315 subjects for whom Lac_{rest} as well as clinical chemistry data, anthropometric data and results from an exercise stress test are available. For these subjects, 10-year cardiovascular risk was calculated using the Framingham score [15]. Subjects with a Lac_{rest} outside the normal range for Lac_{rest} as described below were not excluded from the analysis.

Lactate analysis and clinical chemistry

For lactate analysis, samples were taken at rest before routine ergometer testing using capillary sampling from the hyperemized earlobe. Resting conditions were uncontrolled but performing the resting ECG and echocardiography before the ergometer procedure allowed for a resting period of at least 30 minutes before capillary sampling. During this period, the blood pressure was determined in a supine position using the Riva-Rocci-method on the left arm. Lactate was measured from these hemolyzed whole-blood samples on either Eppendorf EBIOS plus (Wesseling-Berzdorf, Germany) or EKF Biosen analyzers (Barleben, Germany) within a maximum period of up to one hour after withdrawal enzymatic-amperometrically. We calibrated the analyzers before each measurement cycle; hence, the impact of ambient temperature variation in the laboratory is negligible. All lactate analyzers used in our laboratory undergo interlaboratory comparison as requested by German authorities for hospital laboratory analysis (RiLi-BÄK). All other laboratory parameters were obtained from venous blood samples taken before exercise stress testing from an antecubital vein and were either analyzed in our own (full blood count, HDL, LDL) or our hospital's central laboratory (total cholesterol, triglycerides, glucose) by conventional methods. Not all measures were determined in all subjects (see ▶ **Table 1**).

Performance testing

All subjects underwent a graded exercise test on either a bicycle ergometer or a treadmill until subjective exhaustion. was estimated from maximal performance using the ACSM equations. [16].

Statistics

All statistical analyses were performed using R [17]. Reference values for Lac_{rest} were determined using parametric descriptive statistics. To determine whether individual reference ranges for Lac_{rest} are applicable and to obtain a reference to determine effect size, intra- versus inter-subject variability of the respective measures was expressed as ratio r, which was introduced by Eugene Harris [18]. Variance analysis for calculation of r was performed using a linear mixed-effects model fitted by maximum likelihood ("nlme" package, [19]) on a subset of 836 subjects for whom multiple measurements were available for analysis; we analyzed all available replicates).

The Framingham risk score as an estimator of cardiovascular risk [15, 20] was calculated from all available data using the "framinghamriskequation" R package [21] using the "CVD" preset. The Framingham risk score estimates the 10-year-risk for the occurrence of a cardiovascular event (coronary artery disease, stroke, congestive heart failure and peripheral vascular disease) from input variables such as sex and age as well as the lipoprotein profile, the systolic blood pressure, and the smoker status and presence of diabetes. The parameter "left ventricular hypertrophy in ECG" was omitted in calculating cardiovascular risk because left ventricular hypertrophy in our cohort was most probably a benign adaptation to training

A correlation analysis was used to display the raw association between Lac_{rest} and the estimated cardiovascular risk. Cohen's definition of effect size for correlation coefficients [22] was used to describe the effect size of observed correlation coefficient. To account factors confounding the association between Lac_{rest} and the cardiovascular risk, and to investigate the association between Lac_{rest} and other established predictors of cardiovascular risk, linear regression modelling was used. Because of the large sample size, a k-fold cross validation method (with k = 10) could be used for all linear modelling and correlation analyses [23]. We performed all analy-

ses using the "caret" package in R [24]. The descriptive correlation coefficients for the correlation between Lac$_{rest}$ and the cardiovascular risk in the subgroups displayed in ▶ **Fig. 1b–d** were calculated without k-fold-validation. An alpha level of 0.05 was accepted for statistical significance.

Results

Descriptive statistics and intra- to interindividual variation of Lac$_{rest}$

The descriptive statistics for the characteristics of the subjects (n = 9051 samples; 6087 taken from male and 2964 taken from female subjects, mean age 24.6 ± 14.7 years) for each sample taken for this analysis is displayed in ▶ **Table 1a**.

The mean lactate value at rest was 1.16 ± 0.29 mmol·l^{-1}. Based on these values of an apparently healthy group of subjects, the normal range for resting lactate concentration, expressed as mean ± 2 SD, spans from 0.58 to 1.74 mmol·l^{-1}. 3.3 % of all lactate values observed at rest were higher than this observed upper limit of normal in our cohort.

Analysis of intra- to interindividual variation of Lac$_{rest}$ yielded an r value of 3. The intra-individual standard deviation was 0.75 mmol·l^{-1}, the interindividual standard deviation was 0.25 mmol·l^{-1}.

Association between Lac$_{rest}$ and 10-year cardiovascular risk

For this analysis data from 1315 samples (414 female) with a mean age of 37.2 ± 17.2 was analyzed (for further details see ▶ **Table 1b**). Of these, 704 samples were from "endurance" adapted athletes (thereby were 312 leisure time athletes predominantly perform-

ing endurance exercise, 140 road and mountain bike cyclists, 105 track and field athletes, 83 triathletes, 34 Nordic skiers, and 30 from other endurance disciplines), 329 were from "strength/speed" athletes (142 from leisure time athletes predominantly performing strength training, 80 from soccer players, 19 from alpine skiers, 16 from handball players, 15 from track and field athletes from sprint and throwing disciplines, 14 from wrestlers, 11 from tennis players and 32 from other non-endurance disciplines) and 282 form those subjects classified as "sedentary" or sports beginners.

The association between the estimated cardiovascular risk and Lac$_{rest}$ is illustrated in ▶ **Fig. 1a**. Correlation analysis yielded a "low" correlational effect (Spearman's rho = 0.20, p < 0.001) between Lac$_{rest\ and}$ the estimated cardiovascular risk. Analyses of the association between the estimated cardiovascular risk and Lac$_{rest}$ within the subgroups with respect to the different types of predominant training adaptation are displayed in ▶ **Fig. 1b–d**.

The results of the regression analysis investigating the contribution of Lac$_{rest}$ to predicting cardiovascular risk with established risk markers are presented in ▶ **Table 2**. In this linear regression model Lac$_{rest}$ is not a significant predictor of the estimated 10-year cardiovascular risk in our study sample. The association between Lac$_{rest}$ and metabolic parameters determining cardiovascular risk and measures of physical activity, respectively, are illustrated in ▶ **Tables 3** and ▶ **4**. Lac$_{rest}$ is statistically associated with sex, serum glucose, triglycerides, and HDL-cholesterol but not LDL-cholesterol. Moreover, Lac$_{rest}$ is associated with the predominant type of exercise that is conducted by the subject but not aerobic performance per se. Both models feature a "small" effect size of the predictors for explaining Lac$_{rest}$.

Discussion

Lac$_{rest}$ and cardiovascular risk

Recent analyses using a population-based approach are linking atherosclerotic disease with Lac$_{rest}$: Publications based on the ARIC study have highlighted a link between Lac$_{rest}$ with mortality [8], arteriosclerosis [9, 12] and metabolic disease [10]. It was speculated whether this was due to Lac$_{rest}$ pointing towards an "insufficient oxidative capacity" [8].

Our data, based on a young and very fit study group featuring a low cardiovascular risk (median: 1.5 %), also confirms an association between Lac$_{rest}$ and 10-year cardiovascular risk, when Lac$_{rest}$ is used as a single predictor, which is consistent within subgroups of the respective predominant type of exercise (see ▶ **Fig. 1a–d**). However, when parameters of the lipid profile and other known risk modifiers are included in the prediction model, Lac$_{rest}$ does not appear as an independent predictor of cardiovascular risk in our population. This is most probably because in our cohort, a significant association was observed between Lac$_{rest}$ and metabolic factors such as serum glucose, serum triglycerides, and HDL-cholesterol but not LDL-cholesterol (see ▶ **Table 3**). Whilst the present cohort is younger and healthier than the subjects of the ARIC trials, the general finding of an association between Lac$_{rest}$ and the lipoprotein profile was also observed in subjects of the ARIC trial (e. g. [8]). However, the main difference between our study and the reports from the ARIC trial is that in our cohort, Lac$_{rest}$ loses its predictive

▶ **Table 1a** Subject characteristics for samples to create reference range (n = 9051).

a. Sex	6087 male/2964 female
Age (yrs.)	24.6 ± 14.7
BMI (kg/m²)	22.1 ± 3.8
Exercise type ("Endurance"/"Strength/Speed"/"Sedentary")	4670/3624/757
VO2peak (ml/min/kg)	49.6 ± 10

▶ **Table 1b** Subject characteristics of study sample (n=1315).

b. Sex	901 male/414 female
Age (yrs.)	37.2 ± 17.2
BMI (kg/m²)	22.9 ± 3.9
Predominant type of exercise ("Endurance"/"Strength/Speed"/"Sedentary")	704/329/282
VO2peak (ml/min/kg)	43.5 ± 11
Estimated 10-year cardiovascular risk	0.035 ± 0.05 (median 0.015)
HDL-cholesterol (mg/dl)	59.0 ± 14.7
LDL-cholesterol (mg/dl)	127.4 ± 36.4
Serum glucose (mg/dl)	87.1 ± 16.4
Serum triglycerides (mg/dl)	108.6 ± 71.5
Lac$_{rest}$ (mmol/ml)	1.17 ± 0.31
BMI: body-mass-index, Lac$_{rest}$: Lactate at resting conditions.	
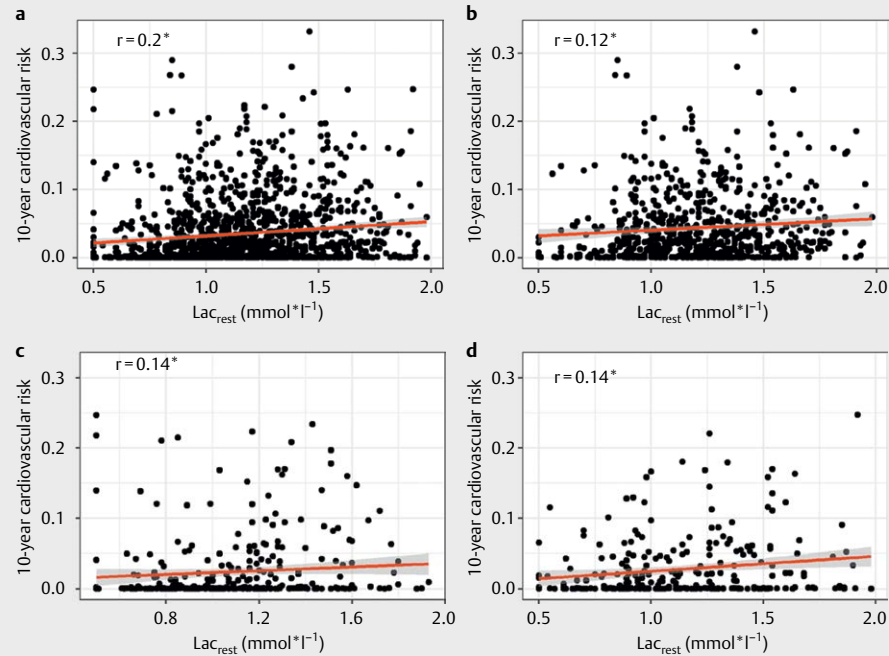
▶ **Fig. 1** Association between Lac$_{rest}$ and cardiovascular risk. Red line = linear fit with confidence interval (standard error) for the slope. **a**: whole study sample (n = 1315); **b**: endurance-type athletes (n = 706); **c**: strength/speed -type athletes (n = 329), **d**: sedentary (n = 284). *: p < 0.05.

▶ **Table 2** Results of linear regression analysis (k-fold validation, k = 10) for explanatory parameters for cardiovascular risk.

	Estimate	Std. Error	t value	P
Intercept	− 12.7900	9.84600	− 1.299	0.194187
Age (years)	2.0090	0.05537	36.288	< 0.0001
HDL-cholesterol (mg/dl)	− 0.7782	0.06033	− 12.900	< 0.0001
LDL-cholesterol (mg/dl)	0.1928	0.02344	8.226	< 0.0001
Sex = female	− 12.7700	2.01300	− 6.344	< 0.0001
Serum triglycerides (mg/dl)	0.0505	0.01142	4.421	< 0.0001
VO$_2$max (ml/min/kg)	− 0.3851	0.10130	− 3.801	< 0.001
Serum glucose (mg/dl)	0.1677	0.04655	3.603	< 0.001
Predominant exercise = "Strength/Speed"	5.7890	2.00300	2.891	0.0039
BMI (kg/m²)	− 0.2212	0.14410	− 1.535	0.1250
Predominant exercise = "Sedentary"	− 3.3200	2.45900	− 1.350	0.1771
Lac$_{rest}$ (mmol/l)	− 0.4694	2.49400	− 0.188	0.8507
R² for final model = 0.7090968. RMSE of cross-validation: 0.0268284. f² = 2.44				
Cardiovascular risk: 10-year-cardiovascular-risk estimated by the Framingham score. BMI: body-mass-index, Lac$_{rest}$: Lactate at resting conditions.				

value for cardiovascular risk when adjusted for confounders, whereas the reports from the ARIC trial yielded significant associations even when fully adjusting for the lipoprotein profile.

Our data illustrates that when studying an association between Lac$_{rest}$ and cardiovascular risk and/or metabolic disease, these associations need to be accounted for not to attribute direct predictive properties to a possibly "bystanding" molecule in the cardiovascular risk profile. The observation of a remarkable intra-individual variability (see below) further supports this notion pointing

towards a rather second-tier role of Lac$_{rest}$ in our cohort when aiming to gain insights concerning cardiovascular risk. In this context, it is important that our healthy study group did not feature relevant cardiovascular disease or diabetes as opposed to the subjects of the ARIC trial.

Interestingly, and without further specification, higher Lac$_{rest}$ values were interpreted as pointing towards impaired oxidative capacity by other researchers speculating on the mechanism by which Lac$_{rest}$ might impact on cardiometabolic disease [10]. Of note, Mat-

▶ **Table 3** Results of linear regression analysis (k-fold validation, k = 10) of explanatory parameters for Lac_{rest} (metabolic parameters).

	Estimate	Std. Error	t value	P
Intercept	0.9463365	0.0632382	14.965	<0.0001
Serum triglycerides (mg/dl)	0.0008238	0.0001262	6.526	<0.0001
Sex = female	−0.1124217	0.0189772	−5.924	<0.0001
HDL-cholesterol (mg/dl)	0.0018476	0.0006213	2.974	0.0030
Serum glucose (mg/dl)	0.0012227	0.0005129	2.384	0.0173
LDL-cholesterol (mg/dl)	−0.0003699	0.0002440	−1.516	0.1298
R^2 for final model = 0.07333333. RMSE of cross-validation: 0.2964259. f^2 = 0 .08				
Lac_{rest}: Lactate at resting conditions.				

▶ **Table 4** Results of linear regression analysis (k-fold validation, k = 10) for explanatory parameters for Lac_{rest} (type of sport and aerobic capacity).

	Estimate	Std. Error	t value	P
Intercept	1.3063134	0.0492455	26.527	<0.0001
sex = female	−0.1150247	0.0192080	−5.988	<0.0001
Predominant exercise = "Strength/Speed"	−0.0839597	0.0210391	−3.991	<0.0001
Predominant exercise = "Sedentary"	−0.0763436	0.0257877	−2.960	0.00313
VO2peak (ml/min/kg)	−0.0014581	0.0009672	−1.508	0.1319
R^2 for final model = 0.04858364. RMSE of cross-validation: 0.2993456. f^2 = 0.05				

sushita and colleagues report a "sports score" which is towards less physical activity in subjects with higher lactate values [8].

The data obtained from our healthy study population do not confirm this link between a reduced oxidative capacity and Lac_{rest}. First, Lac_{rest} is not significantly associated with the maximum oxygen uptake estimated from stress testing, which per definition, is the maximal oxidative capacity of the body during exercise (see ▶ **Table 4**). Second, our analyses show an association (of "small" effect size) between Lac_{rest} and the predominant type of exercise adaptation in our study sample (see ▶ **Table 4**), that is somewhat contrastive to the concept "increased Lac_{rest} – reduced oxidative capacity": while subjects, who conduct predominantly endurance-type exercise showed slightly higher Lac_{rest} values, subjects conducting mostly "strength/speed" -type of exercise appear to have lower Lac_{rest} values. Sedentary subjects feature Lac_{rest} that are somewhere in between the two physically active groups. This points towards other mechanisms of elevated lactate values than a reduced oxidative capacity, as especially endurance athletes would be expected to feature muscle tissue with a higher oxidative capacity [25].

Physiologically, Lac_{rest} values are not necessarily related to oxidative capacity: A relevant proportion of glucose coming from the digestive tract bypasses the liver and is consequently metabolized in peripheral tissues leading to glycolysis and lactate production [26, 27]. The lactate then enters the liver through the bloodstream in the so-called "indirect pathway" [26, 27]. Lac_{rest} is also physiologically linked to the diurnal blood glucose and insulin levels [28]. However, this relation is affected by metabolic disease which might lead to a higher basal lactate production of adipocytes but also deteriorate the capacity of adipocytes to provide lactate in response to glucose ingestion as part of this "indirect pathway" [29]. This

regulation of Lac_{rest} appears to be independent from a so called "oxidative capacity" of muscle tissue and might explain the associations between the relation between Lac_{rest} and cardiometabolic disease that were observed in the ARIC trial.

Possibly, the systematically higher Lac_{rest} levels that we observe in subjects who predominantly conducted endurance training (and most probably therefore feature an excellent oxidative capacity) in our study sample will not have the same physiological basis as the elevation of Lac_{rest} observed in the subjects from the ARIC study featuring increased cardiovascular risk and cardiometabolic disease. In those subjects the observation of an association between Lac_{rest} and cardiometabolic disease might be explained by regarding Lac_{rest} rather as a symptom of an already-manifest, subclinical cardiometabolic condition.

Distribution of Lac_{rest}

To our knowledge, this study is the first to establish normal values for Lac_{rest} in capillary blood based on a larger population of young healthy adults. When comparing the upper limit of normal based on our data, which is 1.74 mmol · l-1, this appears to be slightly lower than the arbitrary threshold of 2.0 mmol · l-1 that is commonly used in clinical practice [30]. Noteworthy, our study sample yielded an effect of sex on Lac_{rest} with female sex being associated with lower lactate values. When comparing the Lac_{rest} values of our cohort with data available from the ARIC publications, most study groups featured lactate values that are compatible with our reference range ([10]: high risk group 1.21–1.63 mmol/l; [9]: considered normal range 0.5–2.2 mmol/l), but some authors observed Lac_{rest} values well above our level of normal ([8], highest included Lac_{rest} 55.5 mg/dl = 6.16 mmol/l). From a methodological point of view, it is relevant that lactate in the ARIC trial was measured from

plasma [8, 11, 31] and not from whole blood as in our study. The difference between our observations and those made from the ARIC study with respect to the association between cardiovascular risk or disease and Lac_{rest} do most probably not arise from systematic differences of Lac_{rest} levels between our study groups.

However, a reference range for Lac_{rest} solely describes between-subject variation. When developing and interpreting reference ranges for a laboratory parameter, the inter- as well as the intra-individual variation must be taken into account [18]. When the intra-individual variability is much lower than the inter-individual variability of a parameter, population-based reference values might not detect all relevant alterations on the individual level.

Our analysis bases on r, the ratio between the intra- and inter-individual variations, which was proposed by Eugene Harris (1974). When r is small (<0.6, "marked individuality"), the intra-individual distribution of measurements is smaller than the overall variance of samples taken from a population. Laboratory parameters with such a small r are suitable for clinical decision making based on individual threshold levels. We observed an r value of 3 in repeated measurements of Lac_{rest} in the same subjects.

For r values ≥ 1.4, the conventional limits include both, measurements of subjects whose intra-individual variations are smaller than average, but also those whose variation values are larger than average [18]. This further illustrates that a Lac_{rest} value within the normal range appears not to be suitable to be included into risk prediction algorithms for the individual "chronic" cardiovascular risk as it does not feature sufficient reliability for all subjects. In this context, it is important to emphasize that the parameter estimates of the associations between Lac_{rest} and predictive variables (with a small but significant effect size) such as sex, lipid parameters, and exercise type are lower than the inter- and intraindividual variation of Lac_{rest} observed in our study sample. Although this may indicate a possible physiological background, the clinical relevance of these observations appears to be dubious. It can be speculated that future investigations aiming to confirm a link between Lac_{rest} and the statistically associated parameters can be improved by vigorously standardizing the carbohydrate intake in the period before the analysis because Lac_{rest} is closely linked to blood glucose and serum insulin levels [29].

Limitations

Per design, this study is unable to establish cause-and-effect relationships. Bias might be introduced by the choice of cardiovascular risk calculation: whilst the Framingham risk score was recommended by the European Society of Cardiology's Guideline at the time of data acquisition [32], it was recently shown that Framingham risk models might overestimate cardiovascular risk in non-US cohorts and subjects at higher risk [33]. Moreover, to our knowledge, the Framingham risk score has not been validated in an athletic population, which on the other hand side holds true for all algorithms for cardiovascular risk prediction. In this context, it is noteworthy that "presence of left ventricular hypertrophy in ECG" was omitted for the calculation of cardiovascular risk, because in this cohort, left ventricular hypertrophy most probably constitutes a benign adaptation to training. However, this might lead to a systematic bias in calculation of the risk model. The population of the present study is on average younger and most probably, much fitter and healthier than the subjects participating in the ARIC studies. Therefore, a direct comparison between the two study samples might be affected by fitness, presence of disease and age, which might hinder direct transferability of our results. As in all observational studies, although adjustments were performed using multiparameter models, we cannot exclude residual confounding.

Conclusion

Our study describes the distribution of blood lactate concentration values at physical rest based on capillary blood samplings in healthy subjects. The results of regression analyses points towards a relation between lactate values at rest with metabolic parameters and the predominant type of exercise, whereas no self-contained predictive property is seen concerning the prediction of the estimated 10-year cardiovascular risk in a young-healthy group of patient-athletes.

Contributer statement

(in accordance to ICMJE recommendations): CA, MW, KR: conception and design, analysis and interpretation of data, drafting and revising the manuscript.

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Conflict of Interest

The authors declares that they have no conflict of interest.

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