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Association of blood lactate with carotid atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Carotid MRI Study

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ABSTRACT

Objectives: Cardiovascular risk factors such as aging, smoking, and insulin resistance may lead to atherosclerosis through various mechanisms of which their association with mitochondrial dysfunction may be one of them. In order to examine this hypothesis, we assessed the association between elevated blood lactate, a marker of mitochondrial dysfunction, and carotid atherosclerosis.
Methods: From a total of 2066 participants from the Atherosclerosis Risk In Communities Carotid MRI study, 1496 were included for this analysis. Wall Thickness and Lipid core presence were measured using gadolinium-enhanced MRI. Blood lactate was categorized into quartiles (Q1: <5.9 mg/dl, Q2: 5.9–7.2 mg/dl, Q3: 7.3–9.2 mg/dl, and Q4: >9.2 mg/dl).
Results: Of the 1496 study participants, 763 (51%) were females, 296 (19.8%) African American, 539 (36%) obese and 308 (20.6%) had diabetes. There was a strong and graded association between lactate and wall thickness [Q1: 1.08 mm (95% CI: 1.01 mm–1.15 mm), Q2: 1.33 mm (95% CI: 1.19 mm–1.47 mm), Q3: 1.44 (95% CI: 1.34 mm–1.54 mm) and Q4: 1.62 (95% CI: 1.53 mm–1.71 mm); p for trend <0.001] after adjusting for age, gender, ethnicity, stature, body mass index (BMI), waist circumference, LDL, High sensitivity C reactive protein (HsCRP), statin use, thiazolidinedione use, hypertension, and diabetes. This association was attenuated, but still significant, after adjusting for a marker of insulin resistance, the triglyceride/HDL ratio, [Q1: 0.96 mm (95% CI: 0.82 mm–1.10 mm), Q2: 1.17 mm (95% CI: 1.08 mm –1.26 mm), Q3: 1.18 mm (95% CI: 1.07 mm–1.29 mm), Q4: 1.22 mm (95% CI: 1.13 mm–1.31 mm), p for linear trend 0.039]. There was no association of lactate with lipid core presence after adjustment for wall thickness.
Conclusions: Blood lactate is associated with carotid atherosclerosis. Attenuation of the association with adjustment for triglyceride/HDL ratio, a marker of insulin resistance, suggests that lactate's association with carotid atherosclerosis may be related to insulin resistance.

Recent evidence implicates mitochondrial dysfunction in the pathogenesis of atherosclerosis. Mitochondrial dysfunction may be related to atherosclerosis due its local effect on the production of reactive oxygen species (ROS) [1] and subsequent oxidized LDL, endothelial cell dysfunction, and increased vascular cell proliferation, a milieu suitable for atherogenesis [1]. In addition, mitochondrial dysfunction is associated with cardiovascular risk factors such as insulin resistance [2–4]. Furthermore, mitochondrial dysfunction is considered an intermediary through which common cardiovascular risk factors such as aging, hyperglycemia, hyperhomocysteinemia and smoking may lead to atherosclerosis [5].

High levels of lactate during exercise indicate low aerobic capacity [6]. In resting individuals, elevated blood lactate is used to indicate primary mitochondrial dysfunction (e.g. hereditary enzyme defects) [2] and insufficient oxygen delivery (e.g. hypoxia and ischemia) [7]. Elevated levels of blood lactate are also indicative of more subtle degrees of low oxidative capacity that occur with obesity and insulin resistance [8–11]. Given the accumulating

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evidence linking mitochondrial dysfunction to atherosclerosis, we hypothesized that mitochondrial dysfunction, as assessed by higher levels of blood lactate, is associated with sub-clinical, stable, chronic atherosclerotic lesions in the carotid vasculature among the participants of Atherosclerosis Risk in Communities (ARIC) carotid Magnetic Resonance Imaging (MRI) Study.

1. Methods and results

1.1. Study population

Study participants were selected from the Atherosclerosis Risk in Communities (ARIC) study cohort [12]. The ARIC study was approved by the institutional review board of the John's Hopkins University, Baltimore, MD. The ARIC study is a prospective predominantly biracial observational cohort of 15,792 individuals aged 45–64 years recruited from a probability sample of four communities (Forsyth County, NC; Jackson, Miss; suburban Minneapolis, Minn; and Washington County, MD). Participants took part in clinic examinations, starting with a baseline visit between 1987 and 1989 and continuing with three follow-up examinations at approximately 3-year intervals, at which point carotid artery intimal medial thickness (IMT) was measured with B-mode ultrasound [13]. Participants in the ARIC carotid magnetic resonance (MR) imaging study were selected from among the surviving ARIC study participants with a disproportionate stratified sampling plan on the basis of the most recent IMT and field center. The goal was to recruit 1200 participants with high values of maximum carotid artery IMT {maximum over six sites: left and right common carotid artery (CCA), carotid bifurcation, and internal carotid artery (ICA)} at their most recent ultrasound examination (examination 3 or 4, performed between 1993 and 1995 or between 1996 and 1998, respectively) and 800 individuals who were selected from among the remaining eligible participants. Field center specific cutoff points of carotid IMT were adjusted over the recruitment period to approximately achieve this goal, with 100% sampling above the cutoff point and a sampling fraction (16.5%–25.5%) below the cutoff point. The cutoff point was 1.135 mm in Forsyth County, NC; 1.000 mm in Jackson, Miss; 1.280 mm in suburban Minneapolis, Minn; and 1.215 mm in Washington County, MD; representing the 73rd, 69th, 73rd, and 68th percentiles of maximal IMT from examination 4, respectively. Persons who were not black or white ($n = 10$ in Forsyth County, NC) were excluded from the selection process, as were those without IMT measurements at examination 3 or 4 ($n = 1428$). In addition, participants with contraindications to MR imaging or contrast media were excluded ($n = 206$), as were participants who had difficulty understanding questions or providing informed consent ($n = 51$), those who had undergone prior carotid revascularization on either side (for the low IMT group) or on the side selected for imaging (for the high IMT group) ($n = 58$), and those who could not participate because of a self-reported health problem ($n = 486$) or another reason ($n = 36$). A total of 4306 persons were contacted and invited to participate in the study. Of these, 1403 declined, 837 were ineligible per above criteria, and 2066 participated (1250 with high IMT, 816 with low IMT). Of the 2066 participants, 1939 had undergone MR imaging, and 1769 MR studies were of sufficient quality and adherence to the MR imaging protocol to merit inclusion. Of these 1639 participants who had no missing data for all MRI variables of interest and lactate measures (described later) were finally included.

1.2. MR imaging methods

A standard MRI protocol was used for all participants and performed on 1.5T scanners (Excite platform, GE Medical Systems, Forsyth County, Jackson, and Washington County, USA; Symphony Maestro, Siemens Medical Solutions, Minneapolis, USA) using bilateral four-element phased array carotid coils (Machnet, The Netherlands). Fourteen MRI technologists, trained centrally and certified by the MRI Reading Center, acquired the scans. Total protocol time was less than 1 h [14,15]. Black-blood MR images were acquired by using a two-dimensional cardiac-gated double inversion-recovery fast spin-echo sequence that was based on a standardized protocol [14] and the following parameters: field of view, 13 cm; section thickness, 2 mm; matrix, 256 × 224; echo train length, 10; one signal acquired; and acquired resolution, 0.51 × 0.58 × 2 mm. Three long-axis black-blood MR imaging sections (repetition time msec/echo time msec/inversion time msec, two R–R intervals/5/600) were acquired through each carotid artery bifurcation by using a time-of-flight MR angiogram as a scout image (Fig. 1). The black-blood MR image that best depicted the bifurcation, including the flow divider, was used to orient all transverse T1-weighted black-blood MR images. The transverse sections were acquired (repetition time msec/echo time msec, one R–R interval/5) with chemical suppression of fat signal before and 5 min after the intravenous injection of gadodiamide (0.1 mmol per kilogram of body weight; Omniscan, GE Healthcare, Princeton, NJ) with a power injector. The inversion time was changed to 200 ms for post-contrast images to enable blood signal suppression. A transverse T1-weighted black-blood MR section was acquired through each distal common carotid artery, positioned 1.5 cm below the flow divider, and oriented perpendicular to the vessel axis (Fig. 1). Sixteen contrast enhanced transverse T1-weighted black-blood MR images (total longitudinal coverage, 3.2 cm) were then acquired through the carotid bifurcation found to have the greatest maximum wall thickness at the participant's most recent US examination. If the contralateral carotid bifurcation wall appeared thicker to the MR imaging technologist on the MR angiographic source images or more stenotic on the MR angiographic maximum intensity projection images, however, this vessel was selected for the multi-section acquisition. The sections were oriented perpendicular to the vessel axis and centered at the thickest part of the carotid bifurcation or through the flow divider if no plaque was present. Analyzes were repeated after excluding 34 vessels that were oriented obliquely (≥25%), with nearly identical results. We used internal carotid artery (ICA) measurements from the section located one section (2 mm) above the flow divider for the present analysis.

1.3. Image analysis

Seven analysts were trained to interpret the MR images with semi-automated software (Vessel MASS; Division of Image Processing, Radiology Department, Leiden University Medical Center, Leiden, the Netherlands). The analysts were blinded to the characteristics of the study participants. All studies were graded for image quality and adherence to the imaging protocol, and studies that failed were not analyzed. Post-contrast black-blood MR images were analyzed by using semi-automated analysis software, as described previously [14,15]. Over the course of the study, 61 randomly selected participants repeated the entire clinic visit including the MRI exam within four to eight weeks to estimate total MRI measurement error from both scan acquisition and reader variability. Both the MRI technologists and the readers were blinded to the repeat participants. Reader reliability was estimated by randomly reassigning scans for interpretation by the same ($N = 53$) or different ($N = 111$) reader. The target interval between readings by the same analyst was at least 90 days to minimize the influence of recall. For linear measurements, our reliability estimates were 0.83 for Wall Thickness (WT), 0.90 for Lumen Area (LA), and 0.89 for identifying lipid core presence [15].