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Association of low-moderate urine arsenic and QT interval: Cross-sectional and longitudinal evidence from the Strong Heart Study☆

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ABSTRACT

Epidemiologic studies suggest that chronic exposure to arsenic is related to cardiovascular disease (CVD), but the pathophysiological link remains uncertain. We evaluated the association of chronic low-moderate arsenic exposure and arsenic metabolism with baseline difference and annual change in ECG measures (QT interval, JT interval, PR interval, QRS duration, and QT dispersion) using linear mixed models in the Strong Heart Study main cohort (N = 1174, median age 55 years) and family study (N = 1695 diabetes-free, median age 36 years). At baseline, arsenic exposure was measured as the sum of inorganic and methylated species in urine (ΣAs) and arsenic metabolism was measured as the relative percentage of arsenic species. Median ΣAs and Bazett heart rate-corrected QT interval (QTc) were 8.6 μg/g creatinine and 424 ms in the main cohort and 4.3 μg/g and 414 ms in the family study, respectively. In the main cohort, a comparison of the highest to lowest ΣAs quartile (>14.4 vs. <5.2 μg/g creatinine) was associated with a 5.3 (95% CI: 1.2, 9.5) ms higher mean baseline QTc interval but no difference in annual change in QTc interval. In the family study, a comparison of the highest to lowest quartile (>7.1 vs. <2.9 μg/g creatinine) was associated with a 3.2 (95% CI: 0.6, 5.7) ms higher baseline QTc interval and a 0.6 (95% CI: 0.04, 1.2) ms larger annual increase in QTc interval. Associations with JTc interval were similar but stronger in magnitude compared to QTc interval. Arsenic exposure was largely not associated with PR interval, QRS duration or QT dispersion. Similar to arsenic exposure, a pattern of lower %MMA and higher %DMA was associated with longer baseline QTc interval in both cohorts and with a larger annual change in QTc interval in the family study. Chronic low-moderate arsenic exposure and arsenic metabolism were associated with prolonged ventricular repolarization.

1. Introduction

The QT interval on an electrocardiogram (ECG) represents the duration of ventricular depolarization and repolarization. Prolonged QT interval has been associated with an increased risk of incident cardiovascular disease (CVD), heart failure, and stroke (Beinart et al., 2014), and a higher risk of fatal CVD events (particularly sudden cardiac death) in both high-risk (Cox et al., 2014) and general populations (Zhang et al., 2011a).

Prolonged QT interval, ventricular tachycardia, and sudden cardiac death are well-known side effects of arsenic trioxide, an inorganic arsenic compound used as a chemotherapeutic agent (Drolet et al., 2004). In experimental studies, arsenic trioxide prolongs the QT interval by disrupting the normal cardiomyocyte action potential, increasing cardiac calcium currents, reducing cardiac potassium channel expression, and inducing cellular calcium

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overload (Drolet et al., 2004; Ficker et al., 2004; Sun et al., 2006). In population-based epidemiologic studies of chronic arsenic exposure, mainly cross-sectional and at high arsenic levels in drinking water (>100 μg/L), higher arsenic exposure was associated with longer QT interval (Ahmad et al., 2006; Chen et al., 2013b; Mordukhovich et al., 2009; Mumford et al., 2007; Wang et al., 2009, 2010; Yildiz et al., 2008).

Hundreds of millions worldwide (Naujokas et al., 2013), including millions of Americans (Ayotte et al., 2011; Hutson et al., 2004; U.S. Environmental Protection Agency, 2013), are exposed to arsenic in water derived from natural geological deposits (National Research Council, 1999). Food (e.g., rice, grains, and juice) contributes to arsenic exposure in most populations, and dietary sources can make up a large proportion of exposure in populations with low-moderate arsenic levels in drinking water (Navas-Acien and Nachman, 2013). Epidemiologic evidence supports an association between chronic arsenic exposure and a higher risk of incident CVD, particularly coronary heart disease (CHD), in populations exposed to high (>100 μg/L) (Chen et al., 2011, 2013a; Sohel et al., 2009) and low-moderate (<100 μg/L) arsenic levels in water (Farzan et al., 2015; James et al., 2015; Moon et al., 2013). Low-moderate arsenic exposure was prospectively associated with an increased risk of CHD and stroke in the Strong Heart Study (SHS), and the association was stronger with fatal events (Moon et al., 2013). The mechanisms explaining that association, however, are uncertain.

In this study, we aimed to estimate the cross-sectional and longitudinal association between chronic low-moderate arsenic exposure and ECG markers of cardiac conduction (QT interval, JT interval, PR interval, QRS duration, and QT dispersion) in the SHS main cohort and ancillary Strong Heart Family Study (SHFS). We also evaluated the cross-sectional and longitudinal association between arsenic metabolism and QT interval. We hypothesized a positive association of arsenic exposure with QT interval, JT interval, and QT dispersion and no association with PR interval and QRS duration based on previous literature (Ahmad et al., 2006; Chen et al., 2013b; Mordukhovich et al., 2009; Mumford et al., 2007; Wang et al., 2009, 2010; Yildiz et al., 2008).

2. Methods

2.1. Study population

The SHS is a longitudinal study of CVD in American Indian communities in Arizona, Oklahoma, and North and South Dakota (Lee et al., 1990). In the SHS main cohort, 4549 men and women 45–74 years old were examined at baseline (1989–91). Surviving participants were examined in 1993–5 and 1998–99 (Visit 2 and 3) (Navas-Acien et al., 2009). In the SHFS, SHS main cohort family members 14 years or older were recruited to participate in a pilot study (1998–99, N = 967), a baseline exam in 2001–2003 (Visit 4, N = 2871), and a follow-up in 2006–2009 (Visit 5, N = 3232) (North et al., 2003). Details of these SHS cohorts have been described previously (Lee et al., 1990; North et al., 2003). We excluded the data of one community that withdrew their consent to participate in further research in 2016. All participants provided informed consent, and the Indian Health Service institutional review board, the institutional review boards of participating institutions, and the participating tribes approved the study protocol.

We restricted the SHS main cohort analysis to 1174 participants free of prevalent CVD (Lee et al., 1990), not using medications with a risk of QT prolongation (Woosley and Romero, 2015), without conduction disorders, and not missing key baseline variables (eFig. 1). At baseline and Visit 2 of the SHS main cohort, 53% and 28%, respectively, of digital ECG records were missing because of a hard disk crash and data transfer errors in the 1990s (Okin et al., 2000). Participants included in the final analytic sample (N = 1174) were largely similar to participants who were excluded because of missing data (eTable 1).

In the SHFS, urine arsenic was measured in participants without diabetes at baseline who were re-examined at Visit 5 and who had enough stored urine for a study of environmental and genetic risk factors of incident diabetes. For this study, the SHFS analysis was further restricted to 1695 participants not using medications that could prolong the QT interval (Woosley and Romero, 2015), without conduction disorders, and not missing key baseline variables (eFig. 2).

2.2. Urine arsenic (inorganic arsenic and methylated metabolites)

The analytical and quality control methods for urine arsenic measurements have been described (Scheer et al., 2012). We used measured arsenic species, including those that directly reflect inorganic arsenic exposure (arsenite, arsenate, monomethylarsenate (MMA), and dimethylarsenate (DMA)), and the generally nontoxic seafood arsenic species (e.g., arsenobetaine) (National Research Council, 1999). The Trace Element Laboratory of the University of Graz (Austria) measured arsenic species in urine using high-performance liquid chromatography coupled to inductively coupled plasma mass spectrometry (Agilent 1100 and 7700x, Agilent Technologies).

In the SHS main cohort, the inter-assay coefficients of variation (CV) using an in-house reference urine for inorganic arsenic, MMA, DMA, and arsenobetaine were 6.0%, 6.5%, 5.9%, and 6.5%, respectively (Scheer et al., 2012). In the SHFS, the CV ranged from 5.4 to 14.4% for inorganic arsenic, 4.8–8.6% for MMA, and 5.5–8.1% for DMA. 5.2%, 0.8%, and 0.03% of samples were below the LOD (0.1 μg/L) for inorganic arsenic, MMA, and DMA, respectively. We imputed concentrations below the LOD as the LOD divided by the square root of two.

We used the sum of inorganic (arsenite and arsenate) and methylated (MMA and DMA) arsenic species (ΣAs) as a proxy for chronic arsenic exposure. The relative percentages of arsenic species over their sum in urine was used as a measure of arsenic metabolism (%iAs, %MMA, and %DMA). To account for variability in spot urine dilution, we divided urine arsenic concentrations by urine creatinine concentrations (μg/g creatinine). We also conducted sensitivity analyses to correct for urine dilution by adjusting for urine creatinine concentrations in regression models or by adjusting urine arsenic concentrations by specific gravity. The latter was conducted only in the subset of participants without diabetes or albuminuria. The results of these sensitivity analyses were consistent with the main analysis (not shown).

2.3. Electrocardiographic markers

A standard digital 12-lead electrocardiogram was performed using MAC-PC or MAC-12 digital ECG systems (GE-Marquette Medical Systems) in the morning of each exam (Okin et al., 2001). QT interval was automatically measured from median complexes using interactive software (QT-Guard, GE-Marquette Medical Systems). QT dispersion was calculated from the difference between the maximum and the minimum QT interval across all leads. QT interval and QT dispersion measurements in the SHS main cohort baseline exam were validated by an investigator (PMO) unaware of clinical data (Okin et al., 2000). JT interval, an alternative measure