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REVIEW ARTICLE

Cardiovascular effects of arsenic: clinical and epidemiological findings

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Abstract Several population studies relate exposure to high levels of arsenic with an increased incidence of ischemic heart disease and cardiovascular mortality. An association has been shown between exposure to high levels of arsenic and cardiovascular risk factors such as hypertension and diabetes mellitus, and vascular damage such as subclinical carotid atherosclerosis. The mechanisms underlying these phenomena are currently being studied and appear to indicate an alteration of vascular function. However, the effects of low levels of exposure to arsenic and their potential detrimental cardiovascular effect are less explored. The article provides an overview of the pathophysiologic mechanisms linking low-level arsenic exposure to the occurrence of cardiovascular disease and its complications, and some potential preventive strategies to implement.

Keywords Arsenic · Cardiovascular disease · Environmental pollution · Drinking water · Oxidative stress · Toxicology

Arsenic (As) is a natural element of the earth's crust whose toxicity has been known for centuries. Adverse effects depend on dose, duration, and frequency of exposure, and can range from neurological and respiratory damage to the onset of cancers of the skin, lung, and bladder (Brunton and Knollmann 2011; Longo et al. 2012); the International Agency for Research on Cancer has classified inorganic As as group 1 human carcinogen (WHO-IARC 2012). Occupational exposure and intentional poisoning are well-known sources of acute toxicity, whereas lower-level long-standing exposures require a broad range of expertise for As detection and the study of environmental fate and mechanisms of human toxicity. The main cause of chronic intoxication for the general population is ingestion of drinking water drilled in deposits contaminated with this metalloid, occurring mainly in developing countries, but also to a lesser extent in the Western world (Lisabeth et al. 2010; Medrano et al. 2010). The World Health Organization and most national legislations have set a limit of 10 μg/L of As in drinking water, corresponding to the reliable detection threshold using current methods, while some countries (especially developing countries) still maintain a threshold of 50 μg/L as recommended by WHO before 1993.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) set a provisional tolerable intake (PTWI) for inorganic As at 2.1 μg/Kg/day or 15 μg/Kg/week (JECFA 1989). The European Food Safety Authority Panel on Contaminants in the Food Chain (EFSA-CONTAM) noted that after this PTWI was established, new data showed that inorganic As causes cancer of the lung and urinary tract in addition to skin, and a range of adverse effects have been reported at exposures lower than those reviewed by the JECFA, concluding that the PTWI of 15 μg/Kg was not appropriate. In 2010, the JECFA withdrew the PTWI (JECFA 2011). The main adverse effects reported by the EFSA-CONTAM Panel associated with long-term ingestion of inorganic As in humans were skin lesions, cancer, developmental toxicity, neurotoxicity, cardiovascular (CV) disease, abnormal glucose metabolism, and diabetes. On the other hand, evidence of CV disease and diabetes in areas with relatively low levels of inorganic As exposure was evaluated as inconclusive (EFSA-CONTAM 2009).

High levels of As exposure in drinking water have been related to increased risk of CV disease. Since this is a major

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cause of death worldwide, and most of the world's population resides in developing countries where the incidence of CV disease is rising, even a modest increase in risk due to As in groundwater might have substantial impact on morbidity and mortality.

The fate of As in the human body

The metalloid As is a natural environmental contaminant. It is present in organic and inorganic form, and in different valence or oxidation states—mainly the trivalent (III) and pentavalent (V). The most toxicologically potent As compounds are in the trivalent oxidation state. Organic arsenicals in the pentavalent oxidation state—such as those used as pesticides, even today—are much less toxic than inorganic ones because unlike inorganic As they are not readily taken up by cells, and undergo limited metabolism (Cohen et al. 2006; Hughes et al. 2011); concern regarding these compounds is due to their progressive breakdown to inorganic As in the environment. As is ubiquitous; diet is the main source of total As for humans, but the organic compounds normally present in food, especially in fish and seafood, are considered nontoxic or of low toxicity. Populations living in coastal areas have on average higher urinary excretion of As than those living inland, without this in itself turning out in toxicity (Delgado-Andrade et al. 2003; EFSA-CONTAM 2009; JECFA 2011; WHO-IARC 2012). Total urinary As is an unreliable marker of exposure to inorganic As, the most toxic form, so studies often adjust this measurement for seafood consumption (Navas-Acien et al. 2008; Kim and Lee 2011; Moon et al. 2012). Soil, air, and absorption through the skin are a minor source of As for the general population, but may be important in professional exposure.

Conversely, As found in water is almost entirely inorganic, and drinking water accounts for most exposure to this form. In water, As is not in its elemental form, which is insoluble, but as arsenate (pentavalent) in surface water, while arsenite (trivalent) is more prevalent in deep anoxic wells (Flora 2011; WHO-IARC 2012). Metabolization in the human body is not completely understood, but the main step is methylation, primarily in the liver, with or without the involvement of glutathione (GSH) (Watanabe and Hirano 2012); most excretion in the urine is in the form of dimethyl, a smaller part as methyl, while about a quarter is excreted as inorganic (Vahter 2000). While methylation is a detoxification process (Huang et al. 2009), some of the intermediate metabolites, particularly those with trivalent As, could mediate some of the toxic and carcinogenetic effects of As.

The precise mode of action of As toxicity is even less well-known. Several modes of action, possibly interrelated, have been proposed as follows: interaction with sulfur and binding to sulfhydryl groups on proteins and enzymes; substitution of arsenate for phosphate, since As and phosphorus both belong to group 15 of the periodic table and share physiochemical properties, cutting off ATP formation in particular; substitution for zinc in zinc fingers; genotoxic action, potentiating the mutagen action of other compounds but also inhibiting DNA enzymatic repair and altering DNA methylation; and alteration of cellular signal transduction (Hughes et al. 2011; Flora 2011). The formation of reactive oxygen species (ROS), also occurring at concentrations that are not directly cytotoxic (Barchowsky et al. 1996), could be the pathogenic mechanism for the observed CV effects.

As and CV disease

Several epidemiological studies in different countries have found a relationship between exposure to high levels of As—as high as >50 μg/L in drinking water, but the limits used to define "high," "moderate," or "low" referring to nonprofessional exposure vary widely—and CV disease. The relationship is particularly evident for peripheral arterial disease ("blackfoot disease" is a form of PAD endemic to areas of Taiwan with extremely high levels of As in drinking water (Tseng 1977)) and coronary heart disease, while the association with stroke is less strong and of borderline significance (Lisabeth et al. 2010; Moon et al. 2012). The studies globally show a temporal sequence between time of exposure and onset of disease, have yielded consistent results in different countries and populations, show a dose–response relation, and show decreased incidence of disease where reduced exposure has been implemented (Chang et al. 2004; Yuan et al. 2007). The association between As and CV disease is at least partly independent of traditional risk factors. Prospective studies do confirm the association (Chen et al. 2011b) and various biological mechanisms for CV toxicity have been investigated; all this is enough to define a causal relationship, i.e., a high level of As exposure is an established risk factor for CV disease (Saposnik 2010; Moon et al. 2012).

Less is known about the CV effects of exposure to lower As levels, closer to the WHO threshold, which interests a much larger population worldwide. Results are conflicting; at these levels, the magnitude of the effect is expected to be smaller, and methodological limitations—mainly the difficulty of assessing actual and cumulative individual exposure, but also the distinction between organic and inorganic As, and outcome measures with the potential confounders—may have played a role in the non-significance of most statistical associations performed so far.

As in the CV continuum

As has been associated in a dose-dependent manner with high blood pressure (Wang et al. 2011; Abhyankar et al. 2012),

even at low levels of exposure (Zhang et al. 2012a), and with renal dysfunction (Chen et al. 2011a) and proteinuria (Chen et al. 2011c). The association with diabetes has been limited to sufficient evidence for high levels (Maull et al. 2012), while some recent data (Jovanovic et al. 2012) conducted with more precise exposure measurements assessing the relation with glucose metabolism (Del Razo et al. 2011) suggest an association even at lower levels (Huang et al. 2011; Maull et al. 2012). The pathophysiological mechanism could be a direct toxic effect on beta-cells, interaction with cellular signaling, or enzyme inhibition in beta-cells or in peripheral tissues (Huang et al. 2011). Consistent with the association with risk factors and CV disease, an association has also been found between As exposure and atherosclerosis (Wang et al. 2002; Wang et al. 2010; Hsieh et al. 2011), and confirmed in experimental animal studies (Bunderson et al. 2004; Srivastava et al. 2009; Lemaire et al. 2011).

Endothelial dysfunction: the link between As and CV disease?

Oxidative stress is an established and widely studied mechanism of As toxicity. ROS are formed both in vivo and in vitro in the presence of As. They include superoxide anion, hydroxyl radical, hydrogen peroxide, reactive nitrogen species, and As-centered and As peroxyl radicals (Bao and Shi 2010b; Hughes et al. 2011; Flora 2011). The mechanisms of ROS formation by As are not completely clear; they may be produced during oxidation of arsenite (III) to arsenate (V) during metabolization, by stimulation of the enzymes NADH or NADPH oxidase (Smith et al. 2001), and NOX (States et al. 2009), or by mobilization of free iron from ferritin (Shi et al. 2004; Flora 2011; Jomova et al. 2011).

Nitric oxide (NO) is one of the main mediators released from the endothelium. It has vasodilatory and anti-inflammatory properties, and inhibits platelet adhesion and aggregation, as well as smooth muscle cell proliferation and migration. ROS inactivate NO and reduce its bioavailability in the vascular endothelium. In addition to the direct action of ROS on NO, As inhibits endothelial NO synthetases (eNOS) (Fig. 1) (Lee et al. 2003; Tsou et al. 2005; Li et al. 2007), depletes GSH—one of the main antioxidant ROS scavengers—and inhibits redox enzymes (catalase, glutathione peroxidase and reductase, thioredoxin reductase, and superoxide dysmutase). The disruption of antioxidant defense mechanisms and the blocking of new NO formation further decrease NO bioavailability and increase endothelial dysfunction (Pi et al. 2000). It is notable that acute exposure or low doses do actually induce redox enzymes, indirectly confirming their role in As detoxification (Shi et al. 2004; Flora 2011). Consistently with the oxidative stress frame, several antioxidants have shown, in vivo or in vitro, a protective effect against As-induced toxicity. These include N-acetylcysteine (Bao and Shi 2010a), alpha-lipoic acid, vitamin C and E, taurine, quercetin (Ghosh et al. 2011), some plant extracts including garlic (Balakumar and Kaur 2009; Biswas et al. 2010; Flora 2011), and resveratrol (Zhao et al. 2008b; Zhang et al. 2012b).

When NO concentrations are reduced, the endothelial surface becomes more prone to atherosclerosis, cell adhesion, and thrombosis, a condition known as endothelial dysfunction, common to all major CV risk factors (aging, hypertension, diabetes, dyslipidemia, etc.) (Deanfield et al. 2007). One of the mechanisms by which As induces endothelial dysfunction is by exaggerating calcium influx in cells (Suriyo et al. 2012). Exposure to As augments endothelial permeability through increased VEGF expression (Bao and Shi 2010a) and reduces proteoglycan synthesis in endothelial cells (Fujiwara et al. 2005); individuals drinking water contaminated with As show dose-dependent expression of plasma levels of cell adhesion molecules, i.e., a pro-atherosclerotic endothelium (Chen et al. 2007). While it is known that As enhances oxidative stress, and that oxidative stress produces endothelial dysfunction, the direct link between exposure to As and endothelial dysfunction in humans has not been investigated extensively. There are no published studies on As and in vivo endothelial function, either in small vessels (venous plethysmography) (Joannides et al. 2006) or conduit vessels (flow-mediated dilation) (Deanfield et al. 2007).

Other mechanisms of CV damage

Endothelial dysfunction characterizes arterial hypertension, and pharmacological blockade of eNOS by L-NMMA raises blood pressure (Owlya et al. 1997), so diminished NO availability is a plausible mechanism to link As with hypertension (Hsueh et al. 2005). Moreover, As decreases in vitro vascular relaxation capability, both endothelium-dependent and endothelium-independent, directly acting on the smooth muscle cells (Lee et al. 2003), while it potentiates response to vasoconstrictors through myosin light chain phosphorylation and Ca^{++} sensitization/inflow (Lee et al. 2005; Li et al. 2010; Lim et al. 2011). Interaction with arachidonic acid biotransformation, influencing vasoconstriction and relaxation, may be another mechanism (Bunderson et al. 2004). Renal damage may be involved in raising blood pressure (Chen et al. 2011c; Hsueh et al. 2009), but the causal relationship with this association remains to be clarified.

As exposure in a wide range of levels is consistently associated with QT prolongation—a risk factor for arrhythmia and sudden cardiac death—torsade de pointes (Ficker et al. 2004; Mumford et al. 2007; Mordukhovich et al. 2009; Wang et al. 2009), and increased QT dispersion (Wang et al. 2010). As may act on QT by increasing cardiac calcium currents

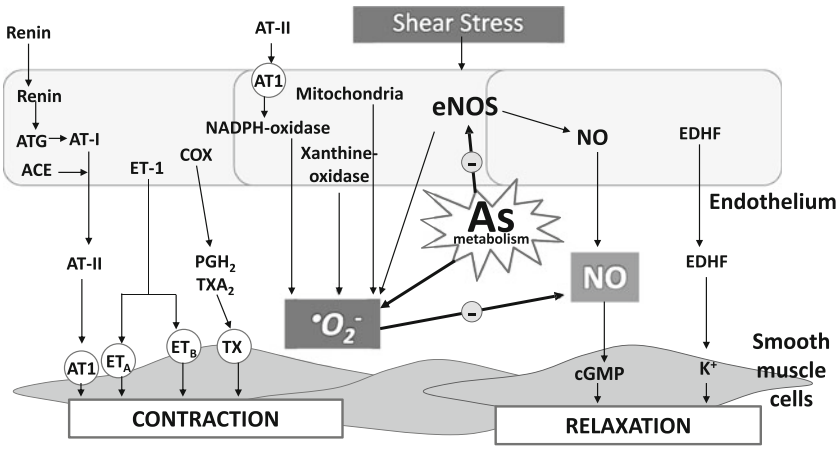

Fig. 1 Arsenic and endothelial dysfunction. *ATG* angiotensinogen, *AT* angiotensin, *ACE* angiotensin converting enzyme, *ET* endothelin, *COX* cyclooxygenase, *PG* prostaglandin, *TX* tromboxane, *NADPH* nicotinamide dinucleotide phosphate, *eNOS* endothelial nitric oxide synthase, *NO* nitric oxide, *cGMP* cyclic guanosine monophosphate, and *EDHF* endothelium-derived hyperpolarizing factors

(Ficker et al. 2004), but no protective effect of calcium antagonists has been found (Mordukhovich et al. 2009), and there are conflicting data on verapamil enhancing or reducing As cardiotoxicity (Zhao et al. 2008a; Luong and Rabkin 2009).

Through the abovementioned mechanisms, As also exerts its direct cytotoxic effects on cardiomyocytes, inducing apoptosis or necrosis (Zhao et al. 2008a; Luong and Rabkin 2009); moreover, the myocardium appears to be a sensitive target tissue for As (Roman et al. 2011). However, population data are scarce, while cardiotoxicity of As_2O_3 as a chemotherapeutic drug is well known, and is more marked in Afro-Americans, probably due to genetic susceptibility (Patel et al. 2006). Specific effects of As on the heart could explain the disproportionate increase in CV events compared to stroke despite the known effect on blood pressure (Zierold et al. 2004; Lisabeth et al. 2010). Although there appear to be no studies regarding a relationship between heart failure or cardiomyopathy and As, there are hints of a synergistic toxic effect of As and alcohol on the heart (Navas-Acien et al. 2006; Bao and Shi 2010b).

Polymorphisms in the genes of enzymes involved in As metabolism, especially As methyltransferase, and in redox enzymes can modulate As toxicity and its CV effects (Vahter 2000; Hsueh et al. 2005; States et al. 2009; Hsieh et al. 2011; Hughes et al. 2011).

Reduced synthesis of extracellular matrix and damage to vascular smooth muscle cells are other mechanisms that could promote atherosclerotic plaque formation and instability (Hays et al. 2008; Li et al. 2010), while oxidation of lipids would make them more prone to be internalized in the vessel wall (Srivastava et al. 2009). As appears to enhance platelet aggregation (Lee et al. 2002), possibly by exposing phosphatidylserine (Bae et al. 2009), though studies are conflicting (Lin et al. 2010), and reduces endothelial fibrinolytic activity by reducing t-PA and increasing PAI-1 level and activity (Jiang et al. 2002), and reduces synthesis of

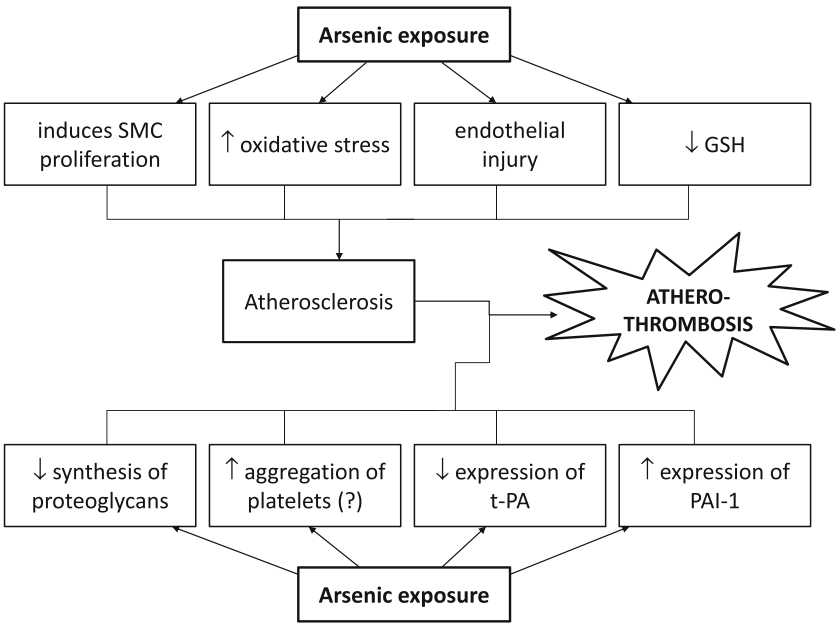

Fig. 2 Arsenic and mechanisms of CV damage. *SMC* smooth muscle cells, *GSH* glutathione, *t-PA* tissue plasminogen activator, and *PAI-1* plasminogen activator inhibitor type 1

proteoglycans such as heparan sulfate (Fujiwara et al. 2005). The activity of As on coagulation and platelets could aggravate thrombosis when the atherosclerotic plaque ruptures (Fig. 2).

CV toxicity of As: diagnosis and therapy

CV toxicity due to As exposure can be suspected based on personal history. Professional exposure is a concern for people working in mines, the wood industry, coal-fired power plants, ore smelting, battery assembly, and electronics. Intentional poisoning was considered a "perfect crime" in the past, since As is odorless and tasteless and symptoms of acute intoxication are quite aspecific, but its use has become rare since As is now detectable in fluids and tissues (Hughes et al. 2011). Contamination of drinking water is usually well-known in particular areas. The patient should be carefully questioned and examined for other As-associated diseases, such as skin lesions and cancers. Hints from clinical history and examination must be confirmed by evidence of As levels in body fluids and tissues indicative of exposure (Das and Sengupta 2008; Marchiset-Ferlay et al. 2012). Since As is metabolized from the blood within a period of hours, blood As levels—normally <1 μg/l—are not a good indicator of long-term exposure, and they are only partially correlated with As in drinking water. The majority of absorbed As is excreted in the urine, normally within 1–2 days, so that urinary As is considered a reliable marker of recent exposure (Jomova et al. 2011). However, as previously mentioned, not all forms of As are (equally) toxic, so total urinary As should be considered only a screening test, or suitable for population studies or continuous professional exposure. Distinguishing organic from inorganic forms, and between oxidation states, requires more complex methods such as chromatographic techniques or spectrometry, and special care in managing the sample—adjusting for seafood consumption, the major source of organic As—is neither reliable nor plausible on a routine basis at the individual level. Studying As in toenails and hair, where trivalent As binds with sulfhydryl groups in keratin, provides information on a more long-term exposure. As species are more stable in these samples, and most of the As is inorganic; on the other hand, the correlation between toenail As and exposure to inorganic As is poor (Hinwood et al. 2003; Slotnick and Nriagu 2006). Variable growth rate of skin appendages could be another confounding factor (Das and Sengupta 2008; Marchiset-Ferlay et al. 2012).

There are no guidelines or consensus statements that tell the clinical cardiologist when to screen for As exposure, but aside from confirmation of exposure suspected on the basis of history or environment, a reasonable approach might be to search for As in patients when arrhythmias or CV events occur without obvious cause or in absence of traditional risk factors.

Patients diagnosed with As poisoning should be promptly removed from sources of the metalloid and provided with supportive measures and specific care for the diseases developed, along with treatment of symptoms and correction of nutritional deficits (States et al. 2009) and electrolyte imbalance, which increases the risk for arrhythmias. The most effective specific treatment for arsenicosis is chelation therapy (Brunton and Knollmann 2011; Longo et al. 2012); however, it is limited to life-threatening conditions due to its potentially severe side effects. Most of the effects of antioxidants have been tested either in vitro, on animals, or (in humans) on soft endpoints (Biswas et al. 2010), but there is some indication of their usefulness as adjunctive therapy during chelation, especially for N-acetylcysteine (Flora et al. 2007).

Conclusions

Several studies suggest CV effects of As exposure at low-to-moderate levels. These effects may translate into a higher CV mortality; however, studies on mortality from CV disease have been inconsistent. Although the mechanisms through which As can cause atherosclerotic lesions and their complications have been explored, individual risks from environmental pollution remain to be established. Many factors make the assessment of such a relationship quite difficult, such as the means of measurement, confounding factors from conventional risk factors for CV disease, and the variability of threshold allowed by individual countries for As pollution. It is time to move from population to individual risk assessment in order to profile the real impact of As exposure at low doses through imaging biomarkers of atherosclerosis. More prospective studies designed to assess doses (thresholds) and risks and individual susceptibility through genetic testing are needed to explore the relationship between As exposure and the occurrence of CV disease and its complications.

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