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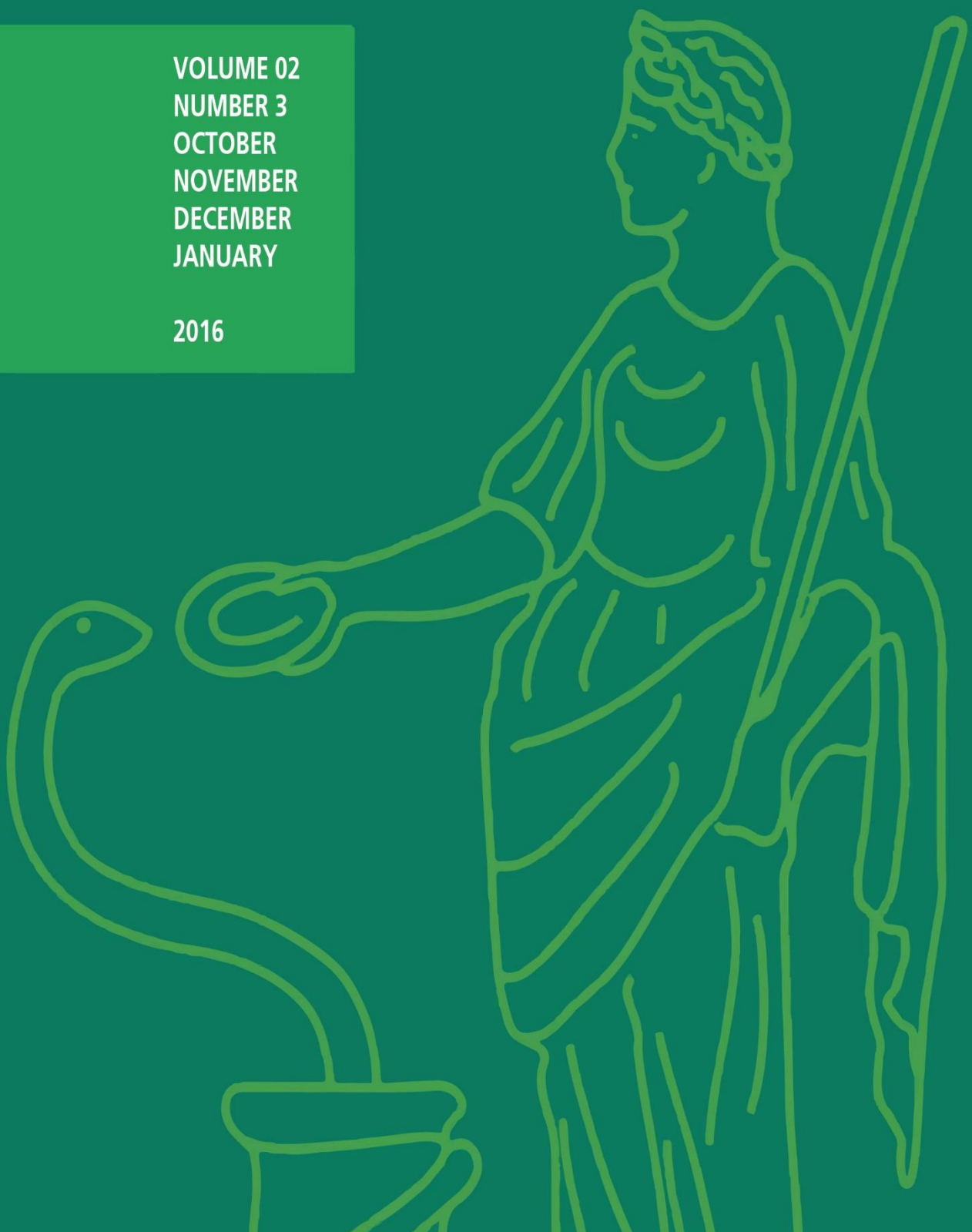

Summary

INSTRUCTIONS FOR AUTHORS

SALUS – Journal of Health Sciences / Revista de Ciências da Saúde
EMESCAM – Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória
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The general publication rules are summarized in the "Uniform Requirements" for Manuscripts Submitted to Biomedical Journals: "Writing and Editing for Biomedical Publication" (www.icmje.org/recommendations). Special suggestions are given to systematic bibliographic reviews and meta-analyzes, retrospective and observational studies on epidemiology, clinical trials, diagnostic accuracy and prospective studies, case reports and case studies. We ask the authors to check the information below before submitting the manuscript to SALUS.

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The Salus – *Journal of Health Sciences* is the scientific magazine by EMESCAM – Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (School of Sciences of Santa Casa de Misericórdia in Vitória) and it is published every four months.

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The following article categories are published in the magazine: original article, editorial, review/update article, case report, brief communication and preliminary note, letter to the editor, experimental work, clinical-surgical correlation and multimedia. The acceptance will be based in originality, significance and scientific contribution. Articles with mere propagandistic or commercial aims will not be accepted. The authors are responsible for the content and information in their manuscripts. The magazine will be fully published in its website (www.salusjournal.org).

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SALUS publishes articles in Portuguese and English and abstracts in Portuguese, English and Spanish.

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Investigations in human beings must be submitted to the Ethics Committee of the Institution, fulfilling the Declaration of Helsinki from 1975, reviewed in 2008. (World Medical Association, available at:www.wma.net/en/30publications/10policies/b3/17c.pdf), and the Resolution CNS 466/12 – Brazilian National Health Council (Conselho Nacional de Saúde), available at http://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf

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1. To have created and planned the activities that led to the work, or interpreted the results found, or both;
2. To have written the work or revised the successive versions and taken part in the revision process;
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1. Study design;
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The use of acronyms must be low. When long expressions need to be repeated, it is recommended that its capital initial letters substitute them after the first mention, which must be followed by the initials between parentheses.

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Title and Authors: The work title, in Portuguese and English, must be concise and

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Abstract (in Portuguese and English): The abstract must be structured in four sections: Objective, Methods, Results and Conclusion. The Abstract in English must follow the same structure of the Abstract in Portuguese. Acronyms must be avoided. The maximum number of words must follow the recommendations of the table (Limits for each article type). The abstract must not be structured in Case Report articles (informative or free). The clinical-surgical correlations and multimedia sections dispense abstract.

Descriptors: Three to five descriptors (keywords) must also be included. The descriptors may be consulted in the electronic address http://decs.bvs.br/, which contains words in Portuguese and English or www.nlm.nih.gov/mesh, for only English words, or in the respective links available at the submission system of the magazine.

Manuscript Body: The Original Articles and Experimental Works must be divided in the following sections: Introduction, Method, Results, Discussion, Conclusion and Acknowledgements (optional). The Case Reports must be structured with the sections: Introduction, Case Report and Discussion; and the Clinical-surgical Correlations must be divided in Clinical Data, Electrocardiogram, Radiogram, Echocardiogram, Diagnosis and Operation. The Multimedia section must present the following sections: Patient Featuring and Description of the Employed Technique. The Review Articles and Special Articles may be structured in sections according to the author's order.

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References

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All authors must be cited in publications with up to 6 authors; in publications with more than 6 authors, the first 6 are cited followed by the Latin expression "et al.".

Titles of journals must be abbreviated according to the List of Journals Indexed for MEDLINE (available at:http://www.nlm.gov/tsd/serials/lji.html).

References Models

Magazine Article

Issa M, Avezum A, Dantas DC, Almeida AFS, Souza LCB, Sousa AGMR. Fatores de risco pré, intra e pós-operatórios para mortalidade hospitalar em pacientes submetidos à cirurgia de aorta. Rev Bras Cir Cardiovasc. 2013; 28(1):10-21.

Organization as Author

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension. 2002;40(5):679-86.

Without indication of authorship

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

Article published electronically before the print version ("ahead of print")

Atluri P, Goldstone AB, Fairman AS, Macarthur JW, Shudo Y, Cohen JE, et al. Predicting right ventricular failure in the modern, continuous flow left ventricular assist device era. Ann Thorac Surg. 2013 Jun 21. [Epub ahead of print]

Article of Internet Journal

Machado MN, Nakazone MA, Murad-Junior JA, Maia LN. Surgical treatment for infective endocarditis and hospital mortality in a Brazilian single-center. Rev Bras Cir Cardiovasc [online]. 2013[cited 2013 Jun 25];28(1):29-35. Available at:http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-76382013000100006&lng=en&nrm=iso

Book Chapter

Chai PJ. Intraoperative myocardial protection. In: Mavroudis C, Backer C, eds. Pediatric cardiac surgery. 4th ed. Chichester: Wiley-Blackwell; 2013. p.214-24.

Book

Cohn LH. Cardiac surgery in the adult. 4th ed. New York: McGraw-Hill;2012. p.1472.

Thesis

Dalva M. Estudo do remodelamento ventricular e dos anéis valvares na cardiomiopatia dilatada: avaliação anátomo-patológica [Tese de doutorado]. São Paulo: Universidade de São Paulo, 2011. 101p.

Legislation

Conselho Nacional de Saúde. Resolução n. 466, de 12 de dezembro de 2012. Dispõe sobre diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos. Bioética. 1996;4(2 Supl):15-25.

Conselho Nacional de Controle de Experimentação Animal. Resoluções n. 12 e 13, de 20 de setembro de 2013. Dispõem sobre a diretrizes brasileiras para o cuidado e a utilização de animais para fins científicos e didáticos (DBCA) e prática de eutanásia.

Other examples of references may be consulted at the website: http://www.nlm.nih.gov/bsd/uniform_requirements.html

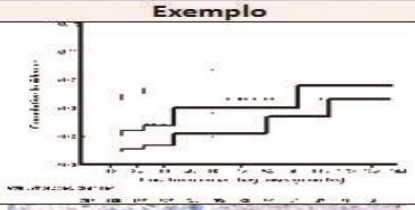
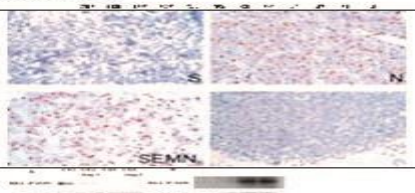
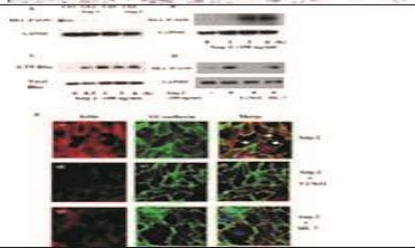
Tables and Pictures

The Tables and Pictures must be numbered according to order appearance in the text, contain a title and be in separate files. The tables must not contain redundant data, previously mentioned in the text. They must be open in the sides and with a totally white background.

The acronyms used in the tables must be mentioned in alphabetical order, in the footnote, with their respective full forms. Similarly, the acronym used in pictures must be explained in the legends.

The pictures will only be published in colors if the author agrees to afford the costs of impression of colorful pages.

Only images in formats TIFF or JPEG will be accepted, with minimum resolution according to the kind of image, for both black and white and colorful images, according to the Table below:

Tipo	Exemplo	Formato	Resolução
LineArt (imagens com linhas lineares, normalmente gráficos com texto)		TIF ou JPG	900 a 1200dpi
Halftone (imagens, normalmente fotografias)		TIF ou JPG	300dpi
Combo (mistura de gráfico e imagem)		TIF ou JPG	500 a 900dpi

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	Original Article	Editorial	Review / Updating Article	Case Report	Case Report and Literature Review	Brief Communication and Preliminary Note	Letter to the Editor	Experimental Work	Clinical-Surgical Correlation	Multimedia
Maximum number of authors	10	4	5	4	6	4	2	10	4	4
Abstract – Maximum number of words	250	-	200	100	100	100	-	250	-	-
Maximum number of words	6,000	1,000	8,000	1,500	3,000	2,000	400	6,000	800	800
Maximum number of references	40	10	75	6	20	6	6	40	10	10
Number of tables and pictures	8	2	8	2	6	2	1	8	2	1
Abbreviated Title	—	—	—	—	—	40 Characters	—	—	—	—

Table Model:

Table 1 – Model table

AREAS	UNESP	UNICAMP	USP	TOTAL
Interdisciplinary	**2**	**2**	**2**	**6**
Biological and Health	**2**	**2**	**2**	**6**
Exact and Technological	**2**	**2**	**2**	**6**
Human and Arts	**2**	**2**	**2**	**6**
TOTAL	**8**	**8**	**8**	**24**

Picture Model:

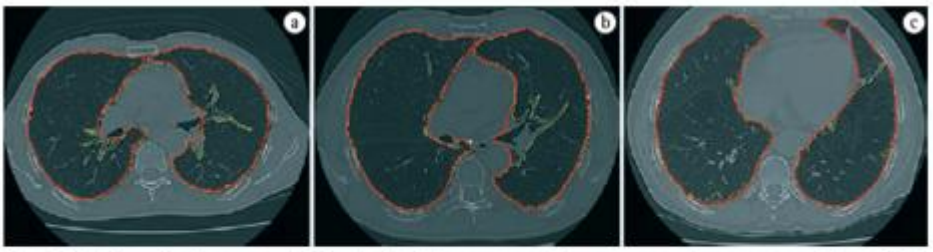

Figura 3 – Exemplos de segmentações classificadas como parcialmente concordantes para o sistema Osiris (contorno amarelo) e o SIStema para a Detecção e a quantificação de Enfisema Pulmonar (SISDEP; contorno vermelho). Sobreposição dos contornos de segmentação em imagens de TCAR em nível de hilo (em a e b) e em nível de base (em c). Em a, a concordância é parcial por imprecisões geradas na segmentação dos dois sistemas; em b, por imprecisão realizada pela segmentação do SISDEP; e em c, por imprecisão ocasionada pela segmentação do sistema Osiris.

Check it before sending the work

- Submission letter indicating the manuscript category.
- Statement by authors and co-authors saying that they agree with the content of the manuscript.
- Approval Letter by the Ethics Committee of Research.
- Manuscript written in software Word 97 or above (formatted to A4); font size 12, space 1.5, font Times New Roman; paged; mathematical symbols and Greek characters using font Symbol.
- Manuscript in the limits adopted by SALUS for its category.

EDITORIAL

The use of heavy metals is closely linked to the history of man. In the prehistory man discovered metals as important materials for the manufacture of utensils and tools. However, the records regarding these metals are not only those who report benefits. Heavy metals such as mercury (Hg), lead (Pb) and cadmium (Cd)are known to be toxic to many organs and tissues of the body (Klaassen, 1992; Clarkson et al., 2003). In this review the main focus will be on exposure to toxic metals, mercury lead and cadmium, when acting ,acute or chronically and even in small amounts, to show that they offer significant risk to public health. Our purpose is to present results obtained from the study of cardiovascular toxic actions of these metals in animal models.

Observations made in the last 15 years by the authors of each review and other reports concerning the effect of trace metals, particularly mercury, lead and cadmium, on animals and man are reviewed with special reference to mechanisms that underlie hypertension and atherosclerosis development.

Among the topics covered similar conclusions are that one common form of toxic effect is the endothelial dysfunction resulting from oxidative stress by reactive oxygen species (ROS) that generates an increased vascular reactivity. These two effects are known to constitute basic mechanisms for hypertension and atherosclerosis development. Our findings, obtained after exposure with doses/concentrations similar or lower than those considered to be safe point towards an important deleterious effect on endothelial function and causing oxidative stress.

Our purpose is that this review, evaluating the toxic effects generated by these three metals, will draw attention to public health that they act as an important risk to human health and in particular the cardiovascular system.

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REVISTA SALUS
JOURNAL OF HEALTH SCIENCES

REVIEW ARTICLE

Toxic effects of mercury on blood pressure and myocardial contractility

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Keywords

Mercury;
Myocardial Contraction;
Toxicity

Abstract

Environmental contamination by heavy metals such as mercury (Hg), cadmium (Cd) and lead (Pb) has exposed humans producing health consequences. Mercury actions are remarkable in this context, due to its high toxicity and high mobility in ecosystems promoting toxicity to many organs and tissues of our body and the health consequences of such exposure are not clearly understood. Mercury have been used for many years in a wide variety of human activities, and nowadays both natural and artificial sources are significantly increasing the exposure to this metal. Several studies show that mercury exposure induces changes in the cardiovascular system, such as hypertension in humans and animals. In isolated myocardium preparations mercury in uM concentrations produces a positive inotropic effect followed by a toxic effect with negative inotropism at higher concentrations. The metal produces potent reducing effect of myosin ATPase activity, and in isolated hearts, promotes reduction of the developed pressure, heart rate and increases the incidence of arrhythmias. On the vessels produced important peripheral and pulmonary vasoconstriction. In anesthetized animals it also lowers blood pressure and causes bradycardia. The blood pressure reduction is due to the development of diastolic heart failure and pulmonary hypertension. In recent years we have focused efforts on the same preparations using nanomolar concentrations of mercury. These concentrations have shown, after some time, toxic effects explained by the fact that the cells concentrated mercury. Moreover, under chronic exposure with mercury for 30 days the cardiovascular effects showed: no increase in blood pressure;

hemodynamic parameters showed a single change, the increased left ventricle end diastolic pressure; in isolated hearts we observed reduction of developed pressure and time derivatives at baseline conditions and in almost all studied diastolic pressures, and decreased β-adrenergic response; the treatment do not change the contractile parameters in left ventricle papillary muscles but increased the activity of myosin Ca2+-ATPase and inhibited the specific activity of Na,K-ATPase; and occurs coronary endothelial dysfunction by increased production of free radicals. The results described in this review indicate that mercury exposure, even at low doses, affects cardiovascular function. As a result, the reference values defining the limits for the absence of danger should be reduced. The results described in this review indicate that mercury exposure, even at low doses, affects cardiovascular function. As a result, the reference values defining the limits for the absence of danger should be reduced.

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Introduction

The use of heavy metals has intimate connection to the history of man. Since prehistoric tools. However, the records relating to metals are not only those who report their benefits. Heavy metals such as mercury (Hg), cadmium (Cd) and lead (Pb) are environmental contaminants and toxic to many organs and tissues of our body.[12,30] Mercury actions are remarkable in this context, due to its high toxicity and high mobility in ecosystems.[36]

Mercury has been used commercially and in medicine for centuries. In the past, several drugs commonly constituted several medicines and today it is still the primary use to preserve vaccines. Even with the knowledge of its toxicity, to a lesser extent, it is still being used in hospital equipments, such as thermometers and sphygmomanometers and commercially, in fluorescent lamps and batteries. Thus, its use leads both to accidental and occupational exposure.[13] Many organomercury compounds were used as pesticides (eventually in an inadvisable form are still employed), others follow with medical applications as an antiseptic (such as the sodium salt of o-ethylmercury acid, commercially known as Merthiolate), and also the metal have been used as mercurial diuretics (Azevedo, 2003).

Mercury is absorbed in the form of vapor (via the pulmonary route) through the gastro-intestinal tract (oral ingestion, soluble form) or through the skin and sebaceous glands (insoluble form), distributing and accumulating in almost all organs and tissues of our body.[11,38] The most common chemical forms, which enable these modes of absorption are as HgCl2, which is soluble in water, the methyl mercury, which is well absorbed by the digestive tract and which commonly accumulates in animals as fishes (hence the absorption by human beings eating these animals) and metallic mercury (which generates vapors or aerosols) can be absorbed due to its high lipid solubility. After absorption Hg concentrates mainly in kidneys and nervous tissue. Its effects are already known on the central nervous system, promoting serious and irreversible damage; on the kidney promoting tubular and glomerular lesions; on the intestines (caustic action of Hg responsible for acute digestive disorders), causing severe

diarrhea by intestinal mucosal injury as well as toxic effects on other organs and tissues (chronic hidroargirism). Chronic mercury poisoning comes from the absorption of small quantities over prolonged periods of time, usually as a result of occupational exposure.

Whereas mercury can be concentrated within the cells, with higher intracellular concentrations than in plasma,[11] our purpose is to describe a series of experimental results about the acute and chronic effects of concentrations observed in individuals exposed to the metal , as those obtained after removal of amalgam fillings on the cardiovascular system, given that today, mercury is widely used in industrial products, various techniques and can be accumulated in food or absorbed in different ways, in the industries of extraction.

The EPA[17] (US Environmental Protection Agency's 1997) recommends mercury reference value in blood being the exposure considered without adverse effect of 5.8 ng/mL (~21,6 nM)[24,37,40] and estimates that each release dental amalgam attains 3 to 17 µg of mercury vapor per day. In individuals with amalgam restoration inorganic mercury concentration in blood is about 4.3 ng/mL (~ 16 nM).[49] People with more than six amalgam restorations have an average of 2.3 ug Hg/g of tissue[8] and may reach in some cases, at 380 ug Hg/g.[20] The blood concentration, reported in non-exposed population is about 3 ng / ml (~ 11 nM)[53] and studies of workers exposed to mercury found blood concentration of mercury 10.8 ± 1.3 ng/mL (~39,6nM) and 1.6 ± 0.2 ng/mL in control subjects.[25] Serum levels in residents of Guizhou province in China, a typical contaminated area was 7.5 ± 3.2 ng/mL (27.5 nM~) while in unexposed individuals was 0.91 ± 0.3 ng/mL.[10] Spanish children, consumers of a diet with fish have mercury concentration in the hair three times higher when compared to children who do not consume fish (1.4 ng/g vs 0.49 ng/g), a concentration which was more than that recommended by EPA (1 ng/g).[16] In the population living in the Amazon basin and using fish as the primary protein feeding source the mercury concentrations in the hair came up to 150 mg/g, and only 2 of 40 studied municipalities have the average mercury concentration below that recommended by the WHO.[4] The WHO considers a concentration lower than 6 g/g of mercury as acceptable in human hair.[53]

The functional changes promoted by mercury are often accompanied by changes in one or more processes involved in the excitation-contraction coupling mechanism as: 1) inhibition of the Na+ - K+-ATPase.[1,2] 2) inhibition of Ca2+ myosin-ATPase.[35] 3) inhibition of the calcium pump of the sarcoplasmic reticulum.[29] 4) inhibition of Ca++-Mg++-ATPase.[46] and 5) reduction of plasma antioxidant capacity and significant increase in circulating free radicals.[26]

Su &Chen[48] showed that methyl mercury promotes a biphasic effect on rat atrial tissue. Initially, when the atrial tissues are exposed to low concentrations (0.5 to 2 ppm) a positive inotropic effect occurs, accompanied by a deficit of contractility as the metal concentration is increased (2 to 50 ppm). These functional findings were accompanied by structural changes in the papillary muscles and atria, as swelling of mitochondria and sarcoplasmic reticulum (SR). Other studies also show how different concentrations of HgCl2 influence the contractile force of papillary muscle and right ventricle strips, alter the kinetics of activatorcalcium; the activity of contractile proteins, the operation of SR.[3,9,14,18,39]

Moreover, considering that little was known about the effects of the metal on the cardiocirculatory activity we started in our laboratory, since 1991, studies of acute toxic effects of mercury on the cardiovascular system. Until then few studies had shown, as described above, that mercury diminishes myocardial contractility and promoting a drop in blood pressure.[43,48] Based on biochemical actions

of mercury, inhibition of activity ATPase (Na, K-ATPase and Ca-ATPase) by interacting with the protein SH groups,[11,32,39,41,42] data from our laboratory showed that the metal has a similar effect as digitalis at low concentrations (0.5 to 1 uM - positive inotropic effect) followed by depression of contractility at higher concentrations.[39,50] These observations are based on the fact that mercury, even at these low concentrations is capable of inhibiting the activity of Na,K-ATPase[11] leading to increased intracellular concentration of Na, which in turn reduces the activity of Na/Caexchanger by increasing intracellular Ca.[5-7] Ca is then picked up by the sarcoplasmic reticulum, increasing its concentration in this organelle. This effect, although small, is capable during the activation of contraction, to promote small increases in the release of activatorCa by the sarcoplasmic reticulum, generating greater contractile response.

An interesting aspect is that the effects on the increase in developed force were in percentage smaller than the effects on the time derivative of the force. It increased earlier and returned to baseline with a mercury concentration that have depressed the force development.[39] As the time derivative is inversely proportional to time we observed that mercury interacts with the ryanodine channel of the sarcoplasmic reticulum and accelerate the release of calcium from the reticulum, which promotes an increase more marked in the time derivative.[9,39] Another aspect observed in the slices of right ventricle was that mercury exposure (20 nM) enhanced the effects of positive inotropic interventions, since the metal increased intracellular calcium concentration.

Studies show that in the cardiovascular system mercury causes a decrease in blood pressure and heart rate, increased PR interval of the electrocardiogram, an increased incidence of arrhythmias and atrioventricular conduction block.[33] On blood pressure and heart rate of anesthetized rats, mercury administration (5 mg/kgof HgCl2, in rats), promotes a significant drop in blood pressure and heart rate.[44] Our results also demonstrated that these effects are accompanied by increased diastolic pressure, both in the left and in the right ventricle, increased right ventricular systolic pressure and the left ventricle systolic pressure reduced. The increase in right ventricular systolic pressure showed a negative linear correlation with the partial pressure of oxygen. Moreover, the reduction of the partial pressure of oxygen promotes pulmonary vasoconstriction, and this finding explains the pulmonary hypertension. However, pulmonary arterial perfusion bed with mercury exposure also showed a significant pulmonary vasoconstriction.[44] Thus, two important effects were contributing to the development of pulmonary hypertension, reduction of the partial pressure of oxygen and the vasoconstrictor effect caused by mercury.

We also confirmed that on the heart, both in isolated preparations and in anesthetized rats, the negative inotropic effect was due to inhibition of the myosin ATPase and a calcium overload associated with an increased production of free radicals. However, in anesthetized animals, the drop in blood pressure caused by mercury acute administration is accompanied with a diastolic heart failure and pulmonary hypertension. The latter fact was the result of a potent vasoconstrictor effect of mercury on the pulmonary vessels.

Interestingly, the bradycardia resulting from the acute exposure to mercury is blocked by atropine. At the same time there is a reduction of the hypotensive and of the negative chronotropic response to acetylcholine. This was due to the fact that the acute administration of Hg promotes an increase of plasma and myocardial cholinesterase activity.[44]

However, the acute exposure to nanomolar mercury concentration increased systolic and diastolic blood pressure, heart rate and

blood pressure reactivity to phenylephrine.[34] Moreover, Cunha et al.[14] showed that the toxic effects of mercury on ventricular contractility is different in the right and left ventricles, as in the first mercury increases contractility fact that contradicts results obtained with left ventricular preparations, from both isolated papillary muscles and with perfused hearts.[39,50] Another interesting finding is that acute mercury treatment (20 mM) in the right ventricle slices promotes potentiation of inotropic effects caused by increased extracellular calcium and β-adrenergic stimulation with isoproterenol.[18] This effect is supported by the mercury inhibition of the sodium pump, which increases intracellular sodium and reduces the exchanger activity of the Na/Ca exchanger increasing intracellular calcium concentration.

In isolated hearts acutely exposed to 20 mM $HgCl_2$ the metal exposure increases the diastolic pressure of the left ventricle[3] and increases dose-dependently (0.1 to 3 mM of $HgCl_2$) this parameter in the right ventricle.[14] Mercury also causes a decrease of isovolumic left ventricular systolic pressure immediately after exposure to 0.5, 1, 2and 10 uM after 30 minutes of exposure to 20 nM.[3,33] However, the metal exposure does not modify the response of the heart to stretch, ie, those hearts have self-preserved the heterometric regulation mechanism.[33]

In addition, mercury has direct actions on blood vessels. In our laboratory, studying the tail vascular bed of rats we reported that mercury has vasoconstrictor actions as a result from the reduction of the endothelium-dependent vasodilator activity and the generation of superoxide anions by stimulating the production of vasoconstrictors derived from the cyclooxygenase pathway.[15] In rat tail arteries, HgCl2 (6 nM) increased the contractile response to phenylephrine and angiotensin II production by activation of the angiotensin converting enzyme.[51]

The results described above were obtained with micro and nanomolar mercury concentrations. However, recently, other studies have shown that mercury concentrations in blood and plasma increase after removal of amalgam fillings[27,28,31] and, in addition, Salonen et al.[45] reported data suggesting a correlation between the consumption of foods with high concentrations of mercury and cardiovascular diseases. Other studies also correlate mercury exposure with increased risk of myocardial infarction and coronary heart disease.[23,54] In inhabitants of Amazon, who are exposed to mercury through frequent fish consumption, there was a strong positive correlation between blood concentrations of Hg and arterial blood pressure.[19]

From 2006, with the aproval of an International Cooperation project from CAPES, with the Universidade Autonoma of Madrid (UAM), Spain, we began studies of chronic actions of mercury at nanomolar concentrations.[52] In this study normotensive Wistar rats received for 30 days, low doses of mercury and underwent blood pressure measurements, metabolic control and then vascular reactivity studies with rings of aorta and mesenteric resistance arteries were performed. Some important results have already been obtained and among them we can highlight the following: At the end of treatment the rats exposed to mercury had blood mercury levels of 7.97 ± 0.59 ng/mL, values compatible with those found in exposed individuals.[52] We did not observe changes in systolic blood pressure. With regard to cardiac and hemodynamic effects of treatment with mercury, for 30 days we observed that the hemodynamic parameters showed a single change, an increased end diastolic pressure of the left ventricle (LVEDP) in the Mercury group compared to control. However, in isolated hearts from the exposed group to HgCl2 we observed, decrease of developed pressure and time derivatives at baseline conditions and in all diastolic pressures studied. The hearts of the Mercury group also showed a decrease in β-adrenergic response.[21,22]

However, chronic treatment with HgCl2 was not able to change the contractile parameters in LV papillary muscles but increased the activity of the myosin Ca2+-ATPase and inhibited the specific activity of Na,K-ATPase. Possibly, the increased of LVEDP *in vivo* and the negative inotropic effect in isolated hearts are due to inhibition of Na,K-ATPase, which causes an increase in intracellular calcium concentration, induce a relaxation defect by calcium overload. Since hemodynamic parameters are preserved *in vivo*, we can speculate that neurohumoral factors are participating in the maintenance of cardiac inotropism and blood pressure. The increased myosin Ca2+-ATPase activity can also be a compensatory mechanism in heart muscle. We also suggest that the occurrence of a decrease in β-adrenergic response is a result of desensitization of cardiac β receptors by a sympathetic increased activation, as a compensatory mechanism during the exposure to $HgCl_2$.

In summary, on the myocardium and coronary vessels the treatment with mercury for 30 days showed.

1) There is no observed increase in blood pressure.

2) Hemodynamic parameters showed a single change, the increased LV end diastolic pressure.

3) In isolated hearts we observed in the group exposed to HgCl2, reduction of developed pressure and time derivatives at baseline conditions and in almost all studied diastolic pressures, and decreased β-adrenergic response.

4) The treatment was not able to change the contractile parameters in left ventricle papillary muscles but increased the activity of myosin Ca2+-ATPase and inhibited the specific activity of Na,K-ATPase.
5) Coronary endothelial dysfunction by increased production of free radicals.

We can conclude that the exposure to low concentration of HgCl2 promotes negative inotropic effect in isolated hearts, relaxation deficit *in vivo*, increased myosin ATPase and inhibition of NKA.

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REVIEW ARTICLE

Acute and chronic effects of lead on resistance vessels

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Lead exposure; Resistance artery; Vascular reactivity

Abstract

Objective: To present an updated narrative review of lead effects on resistance vessels. **Method:** This is a structured narrative review in three distinct phases: 1) preparation of the guiding question: "What are the acute and chronic effects of lead on resistance vessels"; 2) Sampling in the literature and selection of studies; 3) critical analysis of the selected studies. **Results:** we obtained a review of the history, characteristics, levels of lead and legislation, sources of exposure, use, kinetic and distribution of lead in the human body. In addition to the acute and chronics effects of lead on resistance vessels. **Conclusion:** studies show that the effects of lead contribute to cardiovascular changes being a risk factor for the population.

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Introduction

Heavy metals are considered ubiquitous in nature contributing to environmental contamination and consequently constitute a risk factor for human and animal health.[1] It is known that there are about twenty metals considered to be toxic to organisms, among them stand out lead, cadmium, copper and mercury. It is known that even in regions where contamination levels are not sufficient to cause acute poisoning, bioconcentration of these metals in the food chain, for an indeterminate period of time may cause damage to the detectable health.[2] Lead is a toxic element naturally occurring widely used for thousands of years. This is one of the most common contaminants in the environment, due to the numerous industrial activities that favor its large distribution and are therefore one of the main contaminants of the environment.[3,4] Thus, all human beings have lead in their bodies as a result of exposure to exogenous sources.[5] Despite this metal show no physiological function in the body, its toxic effects on humans and animals have been known for a long time for promoting changes in almost all organs and systems of these espécies.[6]

In general, lead affects all organics systems being able to change the hematological[3,7] and immunological systems.[8] This event may occur from intrauterine life, contributing to the development of fetuses and infants with disorders in the immune system, which in adulthood may be more susceptible to allergic problems, infection, cancer or autoimmune disease.[9]

The toxic effects of the metal on the nervous tissue cause encephalopathies (children and adults) and changes in the peripheral nervous system, observed mainly in adults patients.[3,5,7,10] Several studies have shown that lead poisoning in children can produce permanent damage to the nervous system, including learning disabilities and reduced intelligence quotient (IQ);[11] behavioral problems[12-14] and commitment in memory.[15] In addition, several studies have suggested that this metal reduces the physical growth and stature of children.[16,17]

This cation affect the endocrine system coursing with change, for example, the hypothalamic-pituitary-thyroid axis and suprarenal gland.[5,7,18,19]

The renal system is also a target for lead action, therefore, excessive and prolonged exposure to this metal can cause progressive and irreversible kidney disease, such as nephropathy lead, characterized by decreased renal function and most often it is accompanied by hypertension.[3,5,20]

Moreover, this metal is classified by the "International Agency for Research on Cancer" (IARC) as a probable human carcinogen and the kidneys are the organs most susceptible to cancer development in rats exposed to lead. Added to this the fact are the cumulative mechanisms appearance of renal tumors in humans that are also relevant.[21,22]

Regarding the cardiovascular system, there are many studies that report adverse effects of lead, one of the constituents involved as cause of hypertension.[23-26] In this sense, there are several studies that indicate that both occupational exposure and environmental exposure might promote increase in blood pressure.[27-29]

According to data presented by the Ministry of Health (2006), in Brazil there are no reliable records on the number of individuals exposed occupational and environmentally to this metal. Although this is an important risk factor to human health, it is not yet well established actual by the toxicity of this metal in the human body. Moreover, there is no consensus among toxicovigilance agencies regarding the reference values and biological limits allowed for individuals exposed to this metal. Another worrying fact is the lack of information by the population, in general, on the main sources of exposure and the

harmful effects of this metal to the health of individuals.

The main objective of this review is to describe scientific evidence in the literature related to the toxic concentration of lead in the human body and the impact on public health. In addition, it intends to describe the sources of exposure and use of lead by man; demonstrate the kinetics and distribution of this metal in the human body and describe the acute and chronic effects of lead on the cardiovascular system.

Method

This is a narrative review related to the effects of lead exposure on vascular function. We chose this type of review that enables the incorporation of evidence for convenience, by an expertise in the subject, in order to build a body of knowledge on a particular topic of scientific relevance.

The review process was systematized in three distinct phases, the first one on the elaboration of guiding question: "What are the acute and chronic effects of lead on resistance vessels?" The second phase corresponded to the sampling in the literature, which sought to include the broadest possible range of products identified and ensure the variety and magnitude of results.

Accordingly, an electronic check was performed on the LILACS (Latin American and Caribbean) and MEDLINE (National Library of Medicine, United States). The electronic search was performed using the following combinations of Health Sciences Descriptors (DeCS), "lead exposure; blood lead Concentrations; population exposure; effects of lead; vascular reactivity; resistances arteries; mesenteric artery", and was based on the adoption of the following inclusion criteria: indexing studies in their databases in Portuguese, English and Spanish. They were defined as exclusion criteria: production without text available in full or central theme unrelated to the theme study.

The third phase of this review was the critical analysis of the selected studies. The decision of the inclusion or rejection of the studies was based on reading the titles of the selected studies, followed by critical analysis of abstracts, and studies with central topic not related to the proposed theme for review were rejected. In a second analysis, we proceeded to check contents in full, which was guided by the thematic analysis to identify the main ideas presented.

Result / Discussion

- Exposure to the metal as a public health problem: history, characteristics, levels of lead and legislation.

Lead was one of the first metals to be used by man, being known since 3500 B.C., according to archaeological discoveries made in Egypt. There are reports that the Egyptian civilization used lead in minting coins and manufacturing of cosmetics. During the Roman Empire this metal is widely used in the manufacture of pipes for the sewer system; weapons and household items such as cups, bowls and containers for liquids and food; plus aqueducts and tanks for fermentation and alcoholic beverage packaging.[30]

Lead belongs to the chemical family metals of group IVb of the periodic table. Its atomic number is 82, its chemical symbol is Pb.[31] It is a bluish-graymetal, shiny, odorless, malleable, insoluble in organic solvents and corrosion resistant. It is solid at room temperature, melts at 327 °C, vaporization temperature at 1725 °C. It is found in nature in either free form or in combination with various other metals. These properties determine its wide application in industry and commercial importance in the world market.[3,32,33]

As lead is used for so long, the history of poisoning by this metal is also extensive. Hippocrates in the fifth century B.C., was the first to relate the lead intoxication symptoms to their causal factor.[34] Other occupational poisoning reports were pronounced in England in 1883 by workers who used the metal as raw material.[35] The lead poisoning cause one of the oldest occupational diseases, called Saturnism or Plumbism. The lead poisoning term is a reference to God Saturn, idolized in Ancient Rome. Thus, neurological effects of poisoning by the metal were first described in the Roman Empire.[35] Over the years, advances in experimental animals and fish models allow greater understanding of the toxic effects of lead in various body systems.

Currently, several studies suggest lead as a risk factor for the development of cardiovascular, neurological, gastrointestinal, hematologic, renal and other diseases. Therefore, this metal has been considered a serious problem for public health. However, it is still necessary to develop the area of toxicology research not only to increase knowledge of the toxic effects, but also for the development of preventive measures and findings for possible treatments to be used in cases of poisoning by this metal.[4,35,36]

Through various forms of metal exposure, especially occupational, and considering lead a problem for public health, few countries have established a maximum level of lead in the blood above which the person may be removed from work.[31] In the decades of 60 and 70 common levels of maximum 100 µg/dL were found. Currently, these levels were reduced to the range of 40 to 60 µg/dL in different countries.[37]

The Agency for Toxic Substances and Disease Registry (ATSDR)[7] recommends be holding a blood concentration of lead below 30 µg/dL in adults. In occupational exposure environments levels of blood lead concentration should not exceed 60 µg/dL. Moreover, the American Pediatric Association (APA) considers levels of blood lead concentration ≥ 10 µg/dL excessive for children.

In Brazil, according to a regulatory rules 7 (NR7) of the Ministry of Labor (1988),[38] revised in 2013, the normal reference values, which is the value to be found in non-occupationally exposed population, the Biological Maximum Indexes permitted, are respectively 40 µg/dL and 60 µg/dL.[38,39] It is noteworthy thatthe NR-7 (No. 24 of 12/29/94), also determines the annual monitoring toxic effects of lead through medical examinations in exposed workers.

However, it is shown that lead levels in the blood, lower than the values fixed by these organs, can cause alterations in mood, in memory disorders, in verbal association, in visual intelligence and in attention to metal workers exposed, as well as cardiovascular disorders.[36,40]

- Sources of exposure and use

Lead is relatively abundant in the earth's crust, being the fifth most abundant metal on the planet.[41] Their average concentration in the soil is 10 to 20 mg/kg. In the atmosphere, the concentration was estimated at about 0.0005 µg/m^3 in the air and natural surface water the metal concentration is around 0.02 µg/L.[3]

The highest natural sources of lead are volcanic emissions, geochemical weathering and water mist, and the geological sources of lead arethe igneous and metamorphic rocks.[3,31] In addition to these lead sources, soil contamination can through man-made activities (anthropogenic), mainly from the recovery of metal scrap and waste.[31] In Brazil, a secondary source of lead is obtained mainly from the recycling of automotive batteries, industrial and telecommunications.[39] The emission of gases and particulates resulting from the process of production and recycling are the major polluters of the environment. However, recycling is still the

economically activity more feasible for the extraction.[41]

Because of the extensive use of metal, the man is the main target of exposure due to the contact with lead in their activities. Lead is used in over 200 different industrial processes. The alloys and compounds are used in the manufacture of high-tech products such as, protection of nuclear reactors, thin plates of electronic components, welding processes, as well as batteries, paints and dyes, ceramics, cables and ammunition.[42,43]

Lead is used in the form of blades, pipes or cables, providing greater flexibility and corrosion resistance. It serves as a shield against ionizing radiation and is also used as protection in battery manufacturing.[42]

Lead oxides are used in the plates of electric batteries and accumulators, as components in manufacturing rubber (PbO) as ingredients in inks (Pb_3O_4) and vitrified constituent, enamels and glasses. It is estimated that the battery manufacturing accounts for about 70% of world consumption of this metal.[3]

The presence of lead in paint was and is still used in the decoration of interiors and exteriors of homes as well as toys and furniture. Exposure to lead through the paint may occur during manufacturing and continue for many years with the deterioration or paint removal.[44] In Brazil, in August 2008 was published the Law No. 11,762, which regulates the use of pigments and driers based on lead in paints. The law states that paints cannot contain lead in concentrations equal to or greater than 0.06% by weight.[45]

Lead arsenate is used in the manufacture of insecticide; lead carbonate is employed in the synthesis of polyvinyl chloride (PVC); lead acetate is important to use as varnish, antirust paintings, analytical reagent. This metal is also used in fertilizers or agricultural fertilizers, distributed into the environment.[30,31]

The tetraethyl lead was used for a long time in Brazil (1922) in gasoline to increase the power of car engines and get better fuel economy.[46] But since 1978 was banned and in its place is used ethanol.[31]This fact has led to a drastic reduction of the contact with lead of the general population.[47] However, in many countries, there are still places where gasoline is a permanent source of exposure to this metal.

In developed countries, the control of lead pollution sources is being implemented gradually, with an intense action of environmental organizations and public health. In Brazil, control is virtually non-existent due to lack of data on the actual exposure of the population and interest of national supervisory bodies. Therefore, it is necessary studies that show the risks of exposure to greater understanding of our reality and thereby encourage the public health and the Environment authorities in the control actions.[4]

- Kinetics and distribution of lead in the human body

As described above, lead is a metal widely used for thousands of years. It is considered an environmental contaminant due to the numerous industrial activities that favor its distribution. Thus, all individuals have lead in their bodies as a result of exposure to exogenous sources. In order to correlate the amount of environmental lead and its bioavailability with its toxic effects on the body, it is important to understand the continuous interaction between the absorption, distribution, storage and disposal of this metal.[4]

- Absorption

The lead absorption process from environmental sources depends on the amount of metal, the physical and chemical state, in addition to being influenced by host factors (age, genetic, physiological state) and nutritional conditions.[31] Most of lead

enters the human body through the respiratory and gastrointestinal tract and only in its organic form, can enter the body through the skin.[34] the respiratory tract is the main lead absorption through occupational exposure.[31]

- Distribution

Some hypotheses regarding kinetics of lead distribution have been made decades ago by the scientific community. One of the main ideas based on the distribution model in three compartments: blood, soft tissue and mineralized tissues.[7,31] The half-life of this metal in the three compartments is quite different, being estimated at 36 days for the blood, 40 days for soft tissue and 27 years to the bone.[3]

The lead concentration in the blood is less than 2% of the total in the body. The metal present in the blood is distributed among the organs, mainly depending on the affinity for specific tissue. High levels have been found in aorta, liver and kidneys. The retention of lead stabilizes in the soft tissue in adult life and in some organs may decrease with age, but continues to accumulate in the bones and in the aorta throughout life.[5,34]

In adults, approximately 95% of lead body load is in bone. Since this metal is an organic calcium analogue, its primary site of deposition is the bone tissue. Given the long half-life for lead in bone, this compartment serves as an endogenous source of metal for others compartments, long after exposure has ceased.[3,4] The mobilization of this cation to blood compartments, in pregnant women, it is of great importance and constitutes a risk to the fetus and mother.[3]

- Excretion

The excretion of lead in the human body is slow, with a half-life of about 10 years.[34] This metal is excreted by different routes among which include: renal (75-80%) and gastrointestinal (15%) excretion.There are other sources of excretion which together correspond to 8%, they are: sweat, skin peeling, hair, nails and breast milk.[31,48]

- Acute and chronic effects of lead on resistance vessels

Resistance arteries are called as this for presenting a diameter smaller than 500 micrometers. They play a key role in the total vascular resistance and therefore in the maintenance of blood pressure homeostasis.[49] Peripheral vascular resistance is inversely proportional to the vessel radius to the fourth power and therefore reduction of the diameter of these arteries can produce significant increases in peripheral resistance and thereby the blood pressure.[49] In the literature, there are few reports associating the acute or chronic lead treatment to changes in vascular function of resistance arteries.

Studies showed an association between blood lead levels and hypertension in animals and humans.[50-53] Simoes et al.[54] demonstrated that low doses of lead are already strongly associated with the development of hypertension.

The etiology of the lead-induced hypertension is described to be caused by inhibition of Na, K-ATPase[55] by reducing the bioavailability of nitric oxide plus increased endothelial production of endothelin.[56-59] Furthermore, increased production and involvement of free radicals in the metal exposure reduces the bioavailability of NO[60] and depletes the antioxidant reserves,[53,61] or in some cases, causes it to increase in an attempt to minimize the oxidative effects.[61] The increase in ACE activity,[50,62] Cyclooxygenase-2,[54] the endothelial dysfunction[59] has also been reported as changes produced by lead.

In addition to these mechanisms, increased sympathetic nerve activity, reduced baroreflex sensitivity and reduced parasympathetic tone are involved in the lead-induced hypertension.[50,63,64]

Vascular changes introduced by lead exposure are well described in conductance arteries such as the aorta. However, the effects of lead on resistance arteries need to be better defined, in low doses or large doses in acute or chronic exposure.

Skoczynska and colleagues[65] showed that in studies of infusion after norepinephrine administration, the vasoconstriction was more pronounced in mice treated with lead. Furthermore, they showed that small doses of lead enhance the response of alpha receptors and decreased the response of beta receptors in blood vessels.

Studies in animals and humans have demonstrated that exposure to low doses of lead produces hypertension and lead can cause contraction of vascular smooth muscle.[59,66] Watts et al,[67] showed that acute lead exposure in organ bath interacts with PKC in a calcium-dependent and endothelium-independent way to cause the contraction of vascular smooth muscle cells in mesenteric arteries of rabbits.

Recently, Covre et al,[68] evaluated the effects of exposure to low concentrations of lead in lung of mice resistance arteries and showed that the treatment for 7 days at low concentrations promoted an increase in lead deposition in the vascular bed and brought to increased production of superoxide anion in these arteries. Additionally, there was a reduction of vasoconstriction and endothelium-dependent vasodilation to acetylcholine was unchanged. This reduction in contraction was due to increased hyperpolarization by SKCa channels and Kv, probably as a compensatory mechanism for the decreased responsiveness to NO.

Studies Skoczyńska et al.[69] showed that the vascular effect of dopamine in rats intoxicated with lead and cadmium do not change compared with control. However, these metals modify the reactivity of the mesenteric vessels to angiotensin, and prostaglandins, by the pressor action of dopamine. The literature describes the effect of COX-2 derived prostanoids on vascular effects by lead exposure on the vascular reactivity of aorta.[59] It is also known that the presence of COX-2 in the muscle layer of the arteries contributes mainly to change the tone vascular[70] and the increased vascular COX-2 expression is often associated with hypertension.[71,72]

Studies with resistance arteries should be priority. As we see in these few studies, this bed is directly affected by lead exposure and the mechanisms involved in these changes may contribute to explain the increase in blood pressure in animal models and exposed persons.

Final considerations

Lead is a heavy metal, widely distributed in nature and used by man. In view of the extensive documentation of the toxic effects of lead on the cardiovascular system, a more detailed elucidation of cellular targets and mechanisms through which lead exerts its effects must be performed because the metal exposure becomes a health risk with severe physiological consequences. Regarding the effects of lead on the resistance arteries, it is noteworthy that, although few studies have been shown that the metal causes impaired function of these vascular beds, both in acute and chronic exposure to lead. The actions of lead in resistance arteries potentiate the harmful effects of this metal on the cardiovascular system, promoting health risk as high blood pressure. Thus, it is necessary to evaluate the concentration levels established as safe for exposed and unexposed people, to reduce the deleterious effects of this metal for man.

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REVIEW ARTICLE

Effects of chronic exposure to mercury in special circulations

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Abstract

It is well established that exposure to mercury, whether organic or inorganic, is a cardiovascular risk factor. Chronic exposure to mercury is considered a risk factor for the development of different kinds of diseases, and more recently, it was noted that significant deleterious effect that such exposure causes in the vascular system. In this paper we will discuss the effects on coronary, cerebral and superior mesenteric vascular beds.

Exposure 30 days to HgCl2 promotes endothelial dysfunction in coronary arteries, evidenced by reduced bioavailability of NO related to the increased oxidative stress. Cerebral arteries in the same model of exposure to a low concentration of mercury leads to a reduction in bradikinin-induced relaxation and increased serotonin (5-HT) - induced contraction also by reducing the bioavailability of NO. The metal exposure participates for the development of vasospasms in basilar arteries. In addition to changes in vasoconstrictor and vasodilator activity induced by drugs, treatment with mercury also increases the vasoconstrictor response to electrical stimulation. And this change is due to changes in nitrergic and adrenergic modulation in superior mesenteric arteries by reducing the release and bioavailability of NO via nNOS and increased release of superoxide anion and NA.

Occupational or environmental exposure to mercury is an important risk factor for cardiovascular diseases such as hypertension, myocardial infarction and stroke.

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Introduction

Mercury is an environmental contaminant that affects human health.[1]The effects on human health depends on its chemical form, since the sources of exposure, the target organs, toxicity and metabolism are very different.[2]

Occupational exposure to mercury usually results from exposure to inorganic mercury and elemental mercury as vapor. Dentists, dental offices technicians, chlorine and soda industrial workers, miners, measuring and fluorescent lamps equipment industries workers are the main subjects exposed.[3-5]

The concentration of vapor mercury considered safe for chronic inhalation of steam by the WHO is 0.2 g/m3/kg/day. The concentration should not exceed 1 g/m3 in the air per year.[6]

Exposure to organic mercury occurs primarily by ingestion of contaminated fish (methylmercury) and exposure to ethylmercury contained in cosmetics and vaccines containing the preservative thimerosal.[7,8] Brazil is one of the few developing countries that still allow and provide for the population vaccines containing thimerosal.[9] Intrauterine exposure and children have been shown to alter neurodevelopment.[8]

In The Joint FAO/ WHO Expert Committee on Food Additives (2010) has argued that the beneficial effects on child neurodevelopment of fish consumption is reduced when there is contamination with methylmercury.[10]

According to the WHO, people who consume fish and seafood one or more times a day may have mercury concentrations in the hair reaching up to 10 µg/g. However, in individuals who do not normally consume fish, concentrations cannot exceed 1 to 2 µg/g.[11] In Brazil, the recommendation of the Ministry of Health is the intake up to 400 g of fish with a concentration of 0.5 ug/g of mercury consumed per adult weekly.[12]

The cases of severe mercury exposure occurred in Iraq and Minamata (Japan). In Minamata, between the decades of 20 and 60, a Japanese company specializing in the production of acetaldehyde and PVC dumped methylmercury directly on the bay of the city. It is estimated that in four decades were disposed about 150 tons of methyl mercury in the bay, leading to contamination of fish and the contamination of people who eat these contaminated fish. In total, two million people were exposed, 900 people died and 3,000 people suffered "Minamata Disease", which is characterized by severe seizures, psychosis outbreaks, loss of consciousness and coma.[3,13]

In Iraq, between the late 60s and early 70s, another case of population mercury poisoning occurred. Soy beans and barley were treated with mercury fungicides and used for direct production of bread and other foods. After this organic mercury intake in foods made from contaminated grains, 6,900 people were hospitalized, 475 people died and 15 children were born with congenital abnormalities.[14]

In Brazil, the Amazon basin is where there is greater mercury contamination. The concern arising from the metal contamination arose in the 80s by the large amount of metal released into the environment by mining activities started in 1979. The population exposure was given by inhalation of mercury vapor by the

miners and the consumption of fish contaminated with methylmercury.[15]

The consumption of mercury-contaminated fish is an important source of exposure in the Amazon basin. The local population has high concentrations of mercury in the hair, and a positive correlation between mercury exposure and arterial blood pressure.[16]

Elemental mercury and its organic and inorganic compounds can cause serious damage to various organs and tissues of the human body, both after acute and chronic exposure.[17] In the renal system it is responsible for glomerular injury, tubular injury, renal failure and apoptosis.[18] In the gastrointestinal tract, inorganic and metallic mercury cause stomatitis, nausea, vomiting, abdominal pain, anorexia, diarrhea, colitis, necrosis of the bowel wall, hematemesis, excessive salivation and even loss of teeth.[19,20]

In the central nervous system (CNS) the most frequent effects of exposure to inorganic mercury are: irritability, fatigue, behavioral changes, tremors, headache, hearing and cognitive impairment, dysarthria, incoordination and hallucinations. Exposure to methylmercury leads to serious changes in CNS development.[20,21]

Chronic exposure to mercury is considered a risk factor for the development of different kinds of diseases, and more recently, it was noted the significant deleterious effect that such exposure causes to the vascular system. Therefore, it is necessary to know which are the effects as well as the mechanisms of action of mercury on the vascular system. In this paper we will discuss the effects on coronary, cerebral and mesenteric vascular beds.

- Coronary arteries

Wiggers et al. have developed an experimental model of 30 days exposure to $HgCl_2$, in which the treated rat reached a concentration equal to 7.97 ± 0.59 ng/mL.[22] The reference value recommended by the North American Enviromental Protection Agency for blood mercury concentrations without adverse health effects is 5.8 ng/mL or ~ 21 nmol/L WHO provides a lower concentration than 6 g/g of mercury as acceptable in human hair.[23]

Furieri and collaborators showed for the first time, the effects of exposure to low concentrations of HgCl2 for 30 days using this experimental model on the reactivity of the coronary arteries of rats. Even in low concentration the treatment with mercury was able to alter the function of this important vascular bed. The coronary arteries showed higher reactivity to serotonin and also a deficit in relaxation to acetylcholine. The data suggest that these observed effects are due to increased production of oxygen-derived free radicals, especially superoxide, leading to reduced NO bioavailability. Also, by increasing the participation of prostanoids vasoconstrictors derivatives of arachidonic acid-cyclooxygenase cascade.[24]

Confirming previous results in coronary vascular reactivity it was also found that local production in septal coronary arteries is impaired, while there is a significant increase in the generation of superoxide anion. The gene expression of two major isoforms of generating free radicals subunities of NADPH oxidase, the NOX-1 and NOX-4 is increased, suggesting that this is the main source of production of reactive species upon exposure to HgCl2. The gene expression of SOD-2, an important enzyme responsible for tmetabolizing the superoxide anion into H2O2 and molecular oxygen is also increased. When evaluating the morphology of the coronary vessels, it was observed that treatment with HgCl2, besides altering the vascular function and to promote vascular endothelial dysfunction, it was still able to reduce the total vessel area and the area of the lumen.[24]

To elucidate the mechanisms by which occurred endothelial dysfunction, mercury effects were also studied in explanted porcine coronary endothelial cells after exposure for 24 hours to HgCl2. And it was observed that increasing HgCl2 concentration a dependent production of reactive oxygen species took place. After concurrent exposure to some antioxidants known as tempol, apocynin and tiron, a reduction of ROS production occurred suggesting that the main source of these free radicals is the NADPH oxidase. In endothelial cells, increased production of ROS is also related to reduced NO production, as observed after measurement of nitrites and nitrates, the degradation products of NO in cell culture medium. However, the main synthase protein expression responsible for NO production in endothelial cells, eNOS is increased in endothelial cells exposed to HgCl2. This finding seen in conjunction with the reduction of ROS production produced by incubation with L-NAME, a non-selective inhibitor of NOS, shows that besides increasing the expression of eNOS to be compensatory to the reduction of NO, is also contributing to the production of free radicals for uncoupling of eNOS.[24]

- Cerebral arteries

Wiggers et al using the same experimental model of chronic exposure to low concentrations of mercury which mimics human exposure to this metal found in the rat basilar arteries, an increased contractile responses to 5-HT and impaired endothelial-dependent vasodilation. These results suggest that the exposure to this metal causes endothelial dysfunction.[25]

In addition to the endothelial dysfunction the reduced bioavailability of nitric oxide was observed when the concentration response curve to 5-HT was performed in the presence of L-NAME (NOS inhibitor). L-NAME caused a smaller increase the contractile responses to 5-HT in the arteries of rats exposed to mercury when compared to arteries of rats not exposed to the metal featuring reduced bioavailability of nitric oxide. Mercury exposure causes no change in the expression of SOD isoforms.[25]

This study also noted reduction of the contractile response to 5-HT in the presence of Tiron and apocynin (NADPH oxidase inhibitor). In addition, there was improvement in vasodilatory response to bradykinin in the presence of Tiron and SOD. In the presence of indomethacin the contractile response to 5-HT was reduced and improved the vasodilator response to bradykinin. These results suggest the involvement of the increased production of superoxide anion and cyclooxygenase pathway derived prostanoids increasing the contractile response to 5-HT and the worsening of the vasodilator response to bradykinin. This suggests that endothelial dysfunction caused by chronic exposure to mercury chloride, this vascular bed is associated with increased production of reactive oxygen species and products derived from the COX pathway and a consequent reduction of nitric oxide bioavailability.[25]

- Effects on nitrergic and adrenergic innervation in mesenteric arteries

Several studies of our group had shown in many vascular beds, that the chronic exposure affects vascular reactivity. However, there was still a lack in the literature to describe which are the effects of this exposure on vascular innervation. The vascular tone is determined by a balance in the release of many neurotransmitters.[26,27] The mesenteric arteries have nitrergic, adrenergic and sensory innervation, participating in the control of vascular tone in different pathophysiological situations and can be evaluated by electrical stimulation.[28-30]

Blanco-Rivero et al (2011) showed that exposure to low mercury concentration increases the vasoconstrictor response to electrical stimulation in superior mesenteric arteries, as a result of the combined release of noradrenaline, NO and CGRP (calcitonin-related peptide gene). When evaluating the participation of NA in increased vasoconstriction induced by electrical stimulation we observed an increased participation of adrenergic innervation in arteries from treated rats, either by increasing the release and/or change of the response of vascular smooth muscle cells to NA. In addition, there is a reduction of participation nitrergic innervation responsible for the release of NO via nNOS-phosphorylated.[31]

Thus, we can say that in addition to changes in the vasoconstrictor and vasodilator reactivity induced by drugs, the treatment with mercury also increases the vasoconstrictor response to electrical stimulation. And this change is due to changes in nitrergic and adrenergic modulation. It reduces the release and bioavailability of NO, probably by reducing the activity of nNOS, increasing the release of superoxide anion and the release of noradrenaline.[31]

The work of our group showed, for the first time, that exposure to low concentrations of HgCl2, close to that found in individuals who removed dental amalgams, which were exposed to mercury vapor, or routinely consume contaminated fish, was able to cause endothelial dysfunction in coronary and cerebral arteries. And yet change in the participation in nitrergic and adrenergic innervation in superior mesenteric arteries. That is, exposure to this metal, routinely found in the environment and occupational contamination is a major risk factor for cardiovascular diseases such as hypertension, myocardial infarction and stroke.

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REVIEW ARTICLE

Cardiovascular toxic effects of copper

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Copper; Toxicity; Cardiovascular system

Abstract

Objective: To describe the main cardiovascular effects developed by copper. **Method**: This is a narrative review of the literature. **Results**: Copper can act as a cofactor for some enzymes that act on the cardiovascular system, having an important role in the development of atherogenesis in the angiogenic control and the development of cardiac hypertrophy. **Conclusion**: Both the deficiency and contamination with copper can lead to changes in the cardiovascular system. It is undeniable the need for further research that can clarify the effects and mechanisms involved in the changes produced by copper in the heart and blood vessels. However, it is essential that the safe values of the recommended daily intake to be set and define the blood concentrations of this metal to be reviewed.

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Introduction

Copper (Cu) is an essential element necessary for the maintenance and functioning of living organisms.[1] It is the third most abundant metal in the body[2] and plays an important role in human metabolism, mainly acting as a cofactor for the activity of several enzymes.[3] Among these enzymes, we can highlight the cytochrome C oxidase, necessary for aerobic metabolism; Lysyl oxidase, which participates in the synthesis of collagen and

elastin; Dopamine ß-hydroxylase, which plays an important role in the conversion of dopamine to noradrenaline; and superoxide dismutase, an antioxidant enzyme that acts on the conversion of superoxide to hydrogen peroxide.[4]

Copper homeostasis is essential for enzymatic functioning and proper functioning of the body. Metal deficiency may lead to decreased activity of several enzymes, resulting mainly in the development of oxidative imbalance,[5] neurological alterations,[6] hepatic and cardiovascular.[7-9] In addition, although it is an essential micronutrient for man, Cu is toxic at high levels. An overload of this metal easily activates Fenton reactions, resulting in oxidative cellular damage and cell death. Cu toxicity as a result of dietary excess is generally not considered one of the most important sources of exposure to the metal, probably as a result of Cu[10] uptake and excretion control mechanisms.

However, when copper homeostasis is discontinued, pathological conditions can be developed. In addition to metabolic changes, Cu toxicity may result from exposure to excess caused by accident, environmental contamination, the use of bactericidal and fungicidal agents based on copper, and the emission of copper smelting industry.[10,11] In general, copper deficiency or toxicity from metabolic disturbances or exposure to metal may result in serious damage to the human body. Considering that loss of copper homeostasis offersrisks to human health, this review seeks to describe the human exposure to copper and its main effects on the cardiovascular system.

- Copper metabolism

Absorption of copper occurs mainly in the proximal part of the small intestine, where it is transported to the liver through the portal vein. Several parameters affect the dietary Cu absorption rate, including sex, age, type of food and amount of Cu in the diet. It has been shown that copper absorption is higher in women and children and that there are no differences between young adults and older people.[12] After intestinal absorption, 25% of copper remains in the circulation bound to albumin, while the remainder is absorbed by the liver. After absorption into the liver, about 80% of the copper is destined for the blood circulation bound to ceruloplasmin, while the remainder is re-excreted into the gastrointestinal system.[13] The half-life of copper in a healthy individual is approximately 26 days[14] and most of the excretion occurs via the bile duct. There is no evidence that urinary excretion plays a controlling role in Cu homeostasis in response to changes in metal intake.[10]

Under normal physiological conditions, in which the concentration of copper in the body is normal, ATP7A is the enzyme responsible for absorbing copper in the intestine and transporting it to the metal-dependent enzymes. However, when total reserves of intracellular copper increase, ATP7A moves to the cell membrane to promote copper efflux.[15]

In the plasma membrane and in intracellular vesicles, the CTR1 transporter plays a fundamental role in the uptake of copper. This transporter acts to control copper uptake through cellular plasma membranes, whereas extracellular copper elevations induce CTR1 endocytosis to vesicles whereas a decrease in extracellular copper restores CTR1 levels in the plasma membrane.[16] After copper entry into the cell, it binds to cytosolic chaperones that then transfer the copper to specific cellular targets.[17]

Copper homeostasis is essential for the functioning of the body. Changes in copper metabolism are characteristic of some genetic diseases such as Menkes Disease and Wilson's Disease. Menkes disease is characterized by copper deficiency. The main characteristic of Menkes Disease is the low activity of the copper-dependent enzyme (ATPA7). Wilson's disease is characterized by the copper toxicity that

normally affects the severely hepatic and nervous systems.[18] In Wilson's disease, a compromise exists in biliary excretion of copper leading to an accumulation of metal in the liver. When hepatic storage capacity is exceeded, cell death begins, with the release of copper in plasma resulting in hemolysis and copper deposition in extrahepatic tissues.[19]

- Human exposure to copper

In nature, copper emission occurs from natural sources such as dust carried by the wind, volcanoes, forest fires and through the release of copper mines. Cu is one of the most important metals for commercial and industrial application. It is used as a metal alloy for the manufacture of machines, in constructions, in the transport industries and military weapons.[20,21] In addition, it is an important component of white gold and other alloys used for costume jewelry, dental products and cosmetics. It can also be used as an additive in paints, plastics, lubricants and metal coatings. In Africa it is traditionally used in medicinal practices.[22] Due to its high commercial and industrial demand, copper-based products are produced on a large scale and it is believed that this production will expand in the coming years.[23]

In addition to the use of copper in the industrial sectors mentioned above, it is also widely used in bactericidal and fungicidal products in many agricultural crops, which consequently leads to contamination of soils and food that are produced.[24,25] In addition, copper may also be present in potable water and its concentration may vary depending on domestic plumbing systems and groundwater composition. An increase in the acidity of the water may lead to corrosion in copper plating and increase the concentration of the metal in the water.[26]

The concentration of Cu in food varies according to local conditions. Most diets contain enough Cu (1-5 mg) to prevent a deficiency and not enough to cause toxicity. There is little information available on Cu intake and adequacy in populations with specific diets, such as vegetarians and vegans. However, it has been shown that daily Cu intake is 27% higher in vegetarian women than in omnivorous women.[10]

- Recommended daily intake and safe blood concentration

Although copper is recognized as an essential element for the body's functioning, the uncertainties remain over reference values of daily intake for humans. The Recommended Daily Intake in the United States and Canada is 0.9 mg/day, with a tolerable intake level of 10 mg/day for adults aged 19 years or older.[27]

It has been demonstrated that the daily intake of copper can interfere in the body water balance. Daily intake doses below 0.8 mg/day may lead to net losses, while doses above 2.4 mg/day may lead to water retention.[10]

The usual concentration of copper in human plasma is between 0.3-2.1 μg/mL for the intake of 1.4 to 2.0 mg of copper/day.[28] Population studies have shown copper concentrations in healthy individuals of approximately 1 μg/mL.[29,30] A study performed with the Brazilian population showed serum copper concentration of 0.8 μg mL in men and 1.4 μg/mL in women.[30] This difference between the sexes is expected, since it is well known that women, especially those in the 20-60 age group, increased the absorption of copper. Estrogens also directly influence the metabolism of copper, contributing to the increase of plasma levels of this metal. The effects of estrogens on copper levels are also more evident in pregnant women, as they tend to have even higher concentrations.[31]

- Effects of intoxication and deficiency on the human body

As mentioned, copper is an essential metal and its intake in food is important. However, in addition to exposure related to food intake, the population is still exposed to metal because of its occurrence in the environment and its industrial use. Copper concentrations in the body are tightly controlled under physiological conditions so that their excess or deficiency is harmful to the body. In inflammatory conditions, serum copper levels are increased and trigger oxidative stress responses that activate inflammatory responses. Interestingly, changes in copper metabolism, oxidative stress and inflammation are commonly present in several chronic diseases.[32]

Inhalation is one of the most important routes of copper intoxication. Therefore, lung tissue toxicity is of great concern. In vitro studies have indicated that Cu can induce cytotoxicity, oxidative stress and genetic toxicity in cultured human lung cells. Some studies have shown that intratracheal instillation of Cu induces oxidative stress, inflammation and neoplastic lesions in rats.[23]

In addition to pulmonary manifestations, chronic copper toxicity has been known to cause hepatotoxicity and hepatic cirrhosis. As observed in Wilson's disease and in certain metal intoxication conditions, increased copper concentration has contributed to the development of Alzheimer's disease.[33]

It has also been hypothesized that copper accumulation may be related to cognitive decline and changes in the production of humoral and cellular factors of the immune system.[10] Cu-deficient animals show reduced neutrophil and T cell populations, decreased phagocyte and B[10] lymphocyte activity. The production of antibodies by splenocyte T cells is also reduced. In humans, the relationship between Cu intake and immune function is poorly documented.[10]

In addition to the changes in the described systems, intoxication and copper deficiency are also capable of triggering cardiovascular changes. Experimental and epidemiological studies have demonstrated a relationship between exposure to metal and the emergence of some diseases of the cardiovascular system. Some of these relationships and their mechanisms will be described below.

- Effects on the cardiovascular system

Several studies have shown that high copper concentrations are associated with the development of cardiovascular diseases.[34-37] Among these diseases, atherosclerotic disease is one of the most important causes of mortality in the world,[38] characterized by persistent vascular inflammation,[39] low density lipoprotein (LDL) oxidation and free radical formation. In this context, copper (Cu) is an essential micronutrient for the functioning of enzymes that catalyze oxidation reactions of LDL and have been implicated in atherogenesis through mechanisms that involve the signaling pathways of NF-kB activation.[38,40] It has been demonstrated that serum Cu concentration is higher in patients with atherosclerosis, and increases with the severity of the disease.[38] In addition, it has been shown that copper chelation in apoE-mice effectively inhibits the development of atherosclerotic lesion and improves inflammation in the cardiovascular system.[40]

Copper seems to play an important role in controlling the activity of the enzymes nitric oxide synthase (NOS) and guanylate cyclase (GC).[41] In addition to the development of inflammatory reactions in the body and the control of vascular tone.[41] Copper increases the conversion rate of L-arginine to L-citrulline, depending on the presence of extracellular calcium. Extracellular calcium concentration is a prerequisite for the activation of eNOS by agonists. Thus, Cu can affect the intracellular mobilization of Ca and alter the functioning of eNOS.[42]

In addition to regulate the eNOS function, Cu is essential for the functioning of another

important enzyme for the control of vascular tone, Cu / Zn superoxide dismutase (SOD).[43] It regulates the activity of this enzyme in order to control the vasoconstriction caused by oxygen free radicals. Since copper is a cofactor for the functioning of SOD, increased concentrations of the metal could increase the enzymatic activity, while diminished concentrations could lead to a decrease in SOD activity and consequent increase in superoxide production. It has been demonstrated in experimental studies that copper could prevent the development of peripheral vasospasm[44] and that incubation with submicromolar concentrations of Cu impair endothelium-dependent vasorelaxation probably because of the intracellular generation of O2.[45]

Copper is characterized as a required cofactor in all angiogenic signaling cascades, so much so that a metal deficiency causes neovascularization to decrease. In addition, progression of various angiogenic pathologies (eg, diabetes, cardiac hypertrophy, and ischemia) can be traced by measurement of serum copper levels, which are increasingly viewed as a useful prognostic marker.[46] Copper stimulates factors involved in vessel formation and maturation, such as vascular endothelial growth factor (VEGF), which is required for the activation of hypoxia-induced factor-1 (HIF-1), an important transcription factor that regulates Expression of VEGF. The essential role of copper in the production of VEGF makes it important, for example, in anti-angiogenesis therapy, such as the application of copper chelating agents in cancer therapy. However, suppression of angiogenesis is involved in the progression of cardiac hypertrophy, so much so that copper supplementation improves hypertrophic cardiac disease conditions.[47]

In addition to participating in the control of vascular functioning, copper is also essential for cardiac functioning. It has been shown that Cu supplementation restores chronic cardiac hypertrophy induced by pressure overload. The pressure overload generated by constriction of the ascending aorta causes a decrease in Cu levels in the heart along with the development of hypertrophic cardiomyopathy.[48] Overload causes homocysteine buildup in the heart, which is accompanied by copper depletion through the formation of copper-homocysteine complexes and the excretion of the complexes. Copper supplementation recovers cytochrome c oxidase activity and promotes myocardial angiogenesis, along with regression of cardiac hypertrophy and recovery of contractile function.[49] As previously mentioned, Cu increases VEGF levels and promotes angiogenesis in hypertrophic hearts, improving the parameters of cardiac activity.[48]

However, it is sometimes observed that, under chronic ischemic conditions, capillary density is decreased in the heart.[50,51] Epidemiological studies have demonstrated a relationship between copper deficiency and ischemic heart disease. The reasons for this observation are not clear, but investigation has suggested that one of the effects produced by ischemia is the loss of copper in the heart.[52] Copper supplementation can stimulate the transcription activity of HIF-1 (Hypoxia-Induced Factor) and restore angiogenic capacity, leading to increased capillary density in the heart.[53] In addition to the development of cardiac hypertrophy[48] copper deficiency leads to mitochondrial, structural cardiac alterations and changes in oxidative phosphorylation.[54,55] In situations of changes in copper metabolism, such as Wilson's disease, cardiac arrhythmias, diastolic dysfunctions, cardiomyopathies and sudden cardiac death are rare complications, but can be seen mainly in children due to the accumulation of copper in cardiac tissue.[56]

Conclusion

Both deficiency and contamination with copper can lead to changes in the cardiovascular system. There is sufficient evidence that copper can act as a cofactor for some enzymes in the human organism and thus can modify cellular functioning in several systems, having an important role in the development of atherogenesis, angiogenic control and the development of cardiac hypertrophy. There is no doubt that further research is needed to clarify the effects and mechanisms involved with the changes promoted by copper in the cardiovascular system. However, it is critical that safe values of recommended daily intake and blood concentrations of this metal be established.

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REVIEW ARTICLE

Effects of mercury exposure on conductance and resistance vessels

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Mercury; Condutance Artery; Aorta; Resistance artery

Abstract

Exposure to mercury is a pro-inflammatory factor and causes oxidative stress. One of the main sites affected by oxidative stress, due to the development of atherosclerosis, is the aorta. In addition, changes in the reactivity of resistance arteries greatly influence blood pressure. This work aims to show the effects of mercury, in low concentrations, close to those found in environmental or occupationally exposed individuals, in conductance and resistance arteries. These low concentrations of mercury, for 30 days, caused increased vascular reactivity, oxidative stress and inflammation, as well as the reduction of NO bioavailability in both resistance and conductance arteries. Exposure to mercury has an important deleterious effect on vascular function, mainly because it induces endothelial dysfunction and vascular remodeling. This impact can be compared to those produced by traditional cardiovascular risk factors such as hypertension, diabetes and hypercholesterolemia.

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Introduction

Mercury in organic, inorganic and elemental forms is used in various human activities and this causes man to be frequently exposed to this metal. Reports of the toxic effects of mercury are dating from the nineteenth century, however, only after the disasters in Japan (Minamata Bay) and

Iraq in the 70s that more attention has been given to these effects.[1,2]

The toxic effect of this metal is directly related to the type, time and route of exposure, and human exposure often occurs through the consumption of contaminated fish with organic mercury, administration of thimerosal in vaccines and inhalation of mercury vapor from dental amalgams.[3,4]

Initially, it was observed that the renal and central nervous system had their functions affected by the exposure to mercury, however, in the last two decades also alterations in the cardiovascular system have been noticed, among which are highlighted arterial hypertension, carotid atherosclerosis, coronary artery disease and acute myocardial infarction.[5-9] The toxic effect of mercury on these systems is related to the higher generation of reactive oxygen species.[9-11]

In experimental studies, our group has documented that direct infusion of mercury in rat caudal arteries produced a vasoconstriction associated with changes in endothelial function. These changes are evidenced by the reduction of the mediated endothelium-dependent relaxation and the increased production of COX-derived vasoconstricting prostanoids, increased free radical production with consequent reduction of NO bioavailability.[12] In this same arterial bed, nanomolar concentrations of mercury have already promoted increased reactivity to phenylephrine by increasing ACE activity and stimulation of Angiotensin II.[13]

A study conducted by Bastos et al. with the amazonian riverside population showed that almost all the habitants of the 40 cities studied have blood mercury concentrations above the reference values, indicating that human exposure to mercury is chronic and at low doses.[14]

Considering that humans are chronically exposed to mercury and little was known about the effect of this metal on the vascular system, our group developed an experimental model where the rats were exposed for 30 days to low doses of mercury mimecking human exposure to mercury and allowing the toxic effect of mercury on the vascular system to be evaluated.[15]

In the experimental model of chronic exposure to low doses of mercury developed by Wiggers et al,[15] it was observed that at the end of treatment the animal had a blood concentration of mercury of approximately 8 ng/ml (29nmol/L), a concentration similar to that observed in the human population exposed to this metal.[4,16,17] No alteration of systolic blood pressure levels was observed in this model of exposure, however, there was an increase in the plasma activity of the angiotensin converting enzyme (ACE). With this experimental model it was possible to evaluate the vascular function of resistance and conductance arteries.

- Effects in resistance arteries

Peripheral vascular resistance is inversely proportional to the vessel radius to the fourth power and therefore decreases inthe size of these arteries can produce significant increases in peripheral resistance and therefore increased blood pressure.[18] The luminous diameter is determined by the active and passive properties of the vessel. That is, by its morphological and functional alterations.[19]

Wiggers et al, have shown that treatment with low mercury concentration for 30 days induces endothelial dysfunction in resistance mesenteric arteries possibly by increasing oxidative stress, reducing NO bioavailability, and increasing superoxide anion production derived from NADPH oxidase. Among the main results of the functional evaluation, it is highlighted that the chronic exposure to mercury caused: 1) increased vasoconstricting response to phenylephrine and reduced endothelial NO modulation of this response; 2) reduction of ACh-induced endothelium-dependent vasodilatory response; 3) increased superoxide anion production, plasma

malondialdehyde and total antioxidant status; 4) restoration of NO endothelial modulation in the contractile response to phenylephrine and ACh-induced vasodilation in the presence of SOD (superoxide anion scavenger) and apocynin (NADPH oxidase inhibitor).[15]

It is known that cardiovascular changes, such as hypertension, in addition to having oxidative stress and endothelial dysfunction, are accompanied by structural changes in resistance vessels, a process known as vascular remodeling, usually associated to decreases in its diameter.[20-23] Vascular remodeling is a complex process that may involve an increase (hypertrophy), decrease (hypotrophy) or rearrangement (eutrophy) of vascular wall material.[21,24] In the literature, there was no experimental evidence that chronic treatment with HgCl2 could be associated with structural or mechanical changes of resistance vessels. Our study evaluated for the first time the structural and mechanical properties of third order mesenteric arteries of Control rats and treated with HgCl2 in a system for pressurized arteries, which represents one of the most appropriate current methods for this type of study for its approach to in vivo conditions.[25]

The mercury treatment produced a reduction in wall thickness and in the media: lumen ratio of the vessels, as well as an increase in internal diameter, which could be a consequence of a decrease in vascular wall thickness.[15] These parameters correspond to the definition of outward hypotrophic remodeling.[26]

- Conductance arteries

Exposure to mercury, as demonstrated in resistance arteries and other biological systems, is known to be an important cause of oxidative stress and inflammation.[9,11,15,27] Oxidative stress and inflammation are important factors that generate LDL cholesterol which, in conductance arteries, will lead to atherosclerosis.[28,29] Thus, the effects on conductance arteries, such as the aorta, together with the changes observed in resistance arteries are important for the study of metal exposure, since endothelial dysfunction in both are added as factors of cardiovascular risk.

This same experimental model was used to evaluate the effect of mercury on the conductance arteries and, for this, experiments of vascular reactivity were developed in segments of the thoracic aorta. In this vascular bed, it was also observed that exposure to low doses of mercury during 30 days caused an increase in the contractile response to phenylephrine and a lower participation of NO in this response, reduction of the vasodilator response to acetylcholine, increase in superoxide anion production and malondialdehyde levels (MDA). In addition, it was observed that in the presence of apocynin (NADPH oxidase inhibitor) and SOD (superoxide anion scavenger), there was an improvement of the endothelial NO modulation in the contractile response to phenylephrine and an increase in the vasodilator response to acetylcholine. These results suggest that exposure to mercury promoted endothelial dysfunction due to the reduction of NO bioavailability due to the increase in the production of reactive oxygen species by NADPH oxidase.[15]

The participation of the angiotensin II pathway in the vascular alterations caused by mercury had already been observed by our group.[13] Subsequently, other authors have demonstrated that angiotensin II was able to induce COX-2 expression, to increase prostanoid production[30,31] and that contractile prostanoids derived from the COX-2 pathway caused endothelial dysfunction.[32-34] To elucidate the role of angiotensin II and contractile prostanoids derived from the COX-2 pathway in the vascular reactivity of rats exposed to mercury Peçanha et al, conducted experiments on aortic artery segments.

The hypothesis that exposure to mercury promotes a greater participation of the angiotensin II pathway in vascular reactivity was was reinforced because in rats exposed to mercury it was observed: a) increased plasma ACE activity; B) reduction of the contractile response to phenylephrine in the presence of Losartan (AT 1 receptor antagonist). In addition, the presence of indomethacin (non-selective COX inhibitor), NS 398 (COX-2 inhibitor), SQ 29,548 (TP receptor antagonist), furegrelate (TXA2 synthase inhibitor), SC 19,220 (EP 1 receptor antagonist) reduced the contractile response to phenylephrine in aortic segments of rats exposed to mercury and promoted increased gene expression of COX-2 in the aortas of these animals. These results indicate the involvement of the angiotensin II pathway and the COX-2 pathway, especially TXA2 and PGE2, in the vascular alterations (vascular reactivity) caused by mercury contamination.[35]

Later, in a study where chronically exposed rats at low doses of mercury were co-treated with apocynin (nonspecific NADPH oxidase inhibitor), it was demonstrated for the first time that apocynin improved the endothelial function of the aorta from rats chronically exposed to mercury.[31] This effect is due to the prevention of increased oxidative stress, reduction of lipid peroxidation, changes in defense mechanisms and consequent improvement of NO bioavailability. It is noteworthy that treatment with apocynin did not reduce the participation of COX-2-derived prostanoids in the contractile response to phenylephrine. These results reinforce the hypothesis that chronic exposure to mercury promotes a greater participation of these prostanoids and reactive oxygen species in the contractile response of the rat aorta to phenylephrine. In addition, they indicate that mercury acts via two different pathways, COX-2 and NADPH oxidase pathways, independently.[36]

A more recent study from our group showed that the effects of mercury exposure on vascular reactivity is concentration dependent. Since exposure to a concentration 2.5 times greater than the experimental model proposed by Wiggers et al,[15] causes an increase in vascular reactivity of the aorta, but half of the concentration promotes a reduction in the contractile response to phenylephrine. This reduction is probably due to an increase in NO bioavailability as reinforced by the protein expression data of the phosphorylated fraction of eNOS in aortic segments.[37]

However, when mercury (6nM) was added directly to the perfusion medium of aortic arteries, it was observed that there was still an increase in reactivity to phenylephrine due to increased oxidative stress and consequent reduction of NO bioavailability.[38] This concentration is much lower than the plasma concentration achieved by the treatment proposed by our group previously (29nM or 8ng/mL).[15]

That is, the effects shown by Azevedo et al,[37] were surprising, suggesting that chronic and controlled exposure of mercury at concentrations that do not lead to endothelial dysfunction promotes adaptive and protective responses of the arterial vasculature.[37]

These results show the deleterious effects of mercury on the vascular system, even at low concentrations, help to clarify the mechanisms by which this metal exerts its effects and already suggest possible therapeutic pathways.

Exposure to low concentrations of mercury has a negative effect on vascular function, mainly because it induces endothelial dysfunction and vascular remodeling. This impact can be compared to those produced by traditional cardiovascular risk factors such as hypertension, diabetes and hypercholesterolemia. Therefore, mercury can be considered an important risk factor for cardiovascular disease that can participate in the development of cardio and cerebrovascular events. Whether these effects increase the consequences of

traditional risk factors or play a primary role in patients with low cardiovascular risk still needs to be better studied.

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REVIEW ARTICLE

Acute and chronic effects of lead on conductance vessels

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Lead acetate; Vascular reactivity; Hypertension

Abstract

This study aims to demonstrate the main effects of lead exposure on the vascular system emphasizing actions on conductance vessels. For this purpose, a narrative review was carried out with two main axes: 1) guiding question: which are the effects of acute and chronic exposure to lead on conductance vessels in humans and experimental animals: 2) review of the literature and selection of relevant studies related to this subject. The studies presented in this review showed that lead, regardless of the time of exposure, promotes vascular alterations that are directly associated with an increase in blood pressure contributing to the development of arterial hypertension. Another important aspect is that in all the studies that were performed in the blood analysis after exposure to lead, values well below those recommended as safe by the toxicovigilance agency of Brazil and other countries were found. Research carried out in humans and experimental animals shows lead as an important risk factor for the development of cardiovascular diseases, and it is necessary to reduce the levels of exposure, recommended as safe, for the general population.

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Introduction

Lead presents a high toxicity capable of promoting adverse effects on the human body. This metal is stored in the bones where it causes changes[1] and can be stored in soft tissues such as: kidneys; adrenal glands; pancreas; gallbladder; ovaries; prostate; testicles, heart, blood vessels and skeletal muscle. The concentrations of this cation in these tissues appear to be constant throughout life, due to their high turnover rate.[2] The toxic effects of lead are potentiated by factors such as age, nutritional factors due to iron deficiency and malnutrition, and the presence of concomitant diseases.[3]

Exposure to lead is widely recognized as a common occupational and environmental health problem.[4] Clinical and epidemiological studies show a correlation between blood lead concentration and blood pressure. This is true even at low concentrations, such as 10 to 25 μg / dL Pb-S,[5] similar to the values observed in a population exposed to this metal environmentally.[6-8] The harmful effects of this metal on the cardiovascular system, with the development of diseases, compromise this system, producing changes in blood pressure[8,9] coronary artery disease, myocardial infarction and peripheral arterial disease.[9,10]

According to the World Health Organization (WHO), cardiovascular diseases are currently the leading cause of mortality and morbidity in the world[11] and exposure to toxic agents, including lead and other metals, may contribute to the onset or impairment of these pathological processes. Population studies about the cardiovascular effects of lead are focused on the association between its exposure and the development of hypertension. On the other hand, researches in experimental animals seek to elucidate, in addition to the hypertensive effect, the mechanisms involved in the cardiovascular alterations promoted by this metal.[9]

It should be emphasized that when analyzing the effects of lead on the vascular system, the type of vascular bed studied (resistance or conductance) should be considered. In addition, other factors such as: dose, time and route of exposure to the metal must be observed, since all of them influence in a different way the results provoked by this cation in the biological organisms.

In this review will be emphasized the toxic effects of lead, on conductance vessels, especially the aorta artery. We will present studies in humans and experimental animals that demonstrated the relationship between acute and chronic exposure to this metal with vascular diseases.

- Acute and chronic vascular effects of lead in humans and experimental animals

Furchgott & Vanhoutte[12] described for the first time the role of the endothelium in the regulation of vascular tone. From this study blood vessels are no longer seen merely as conductors of humors in the circulatory system. It is now known that the endothelium is able to release metabolically active substances, which modulate important functions in the body such as vasomotor tone control, vascular caliber, blood flow and also participates in the control of inflammatory and immune responses.[12,13] In fact, the functions of the vascular system imply complex interactions between endothelium, vascular smooth muscle, immune system, nervous system. Moreover, these bonds are present in the chemical and metabolic processes of individual organs.[14-17]

In this sense, several studies have pointed out that the toxicity of heavy metals (lead, mercury, cadmium, copper, arsenic) targets the vascular system promoting damage ranging from hemorrhagic lesions to other pathological processes including edema, atherosclerosis and arterial hypertension. In addition, the vascular effects of these elements can act on specific organs

impairing the metabolic processes and cellular remodeling.[18-22]

Several mechanisms have been proposed to explain the genesis of arterial hypertension caused by lead mainly involving interactions of this metal with endogenous regulatory processes present in endothelial cells and vascular smooth muscle. These factors include: inhibition of Na^+/K^+ -ATPase; Increased renin-angiotensin system activity,[23-27] endothelial dysfunction,[27-29] and vascular smooth muscle.[30-36]

In recent decades, lead-related research has focused on its direct and / or indirect effects on vascular structure, both in studies in humans and in experimental animals. However, there is still no consensus among the authors regarding the pathways of action of lead in the biological organism.

Barbosa Jr. et al,[4] studied 62 volunteers living in the city of Bauru (SP- Brazil) who were exposed to lead in the environment. These authors demonstrated a negative correlation between plasma nitrite and lead present in the plasma and blood of these volunteers, suggesting that this metal promotes an inhibitory effect on the formation of nitric oxide (NO). This finding is supported by other studies whose results have shown that measurements of plasma nitrite concentration reflect the activity of the enzyme nitric oxide synthase (NOS).[37-39] Den Hond, et al,[40] using data from the Third National Health and Nutrition Examination Survey (NHANES III) found a positive correlation between lead concentration and increased blood pressure in black women and men.

In a series of studies conducted in our laboratory we have demonstrated that acute and chronic exposure to lead increases the blood pressure of rats associated with vascular dysfunction.[41,42]

These studies revealed differentiated responses depending on the time and route of exposure to lead. Silveira et al.,[43] verified the acute effects of lead in the caudal bed of rats acutely exposed to high concentrations of lead (100 µM). The findings of this study reveal an increase in the reactivity of the caudal arteries to phenylephrine (α 1 - adrenergic agonist). This response was dependent on the endothelium and the functional changes observed in these arteries suggest the local involvement of the following pathways: nitric oxide; Cyclooxygenase and reactive oxygen species. The main findings of this study can be verified in figure (1) below.

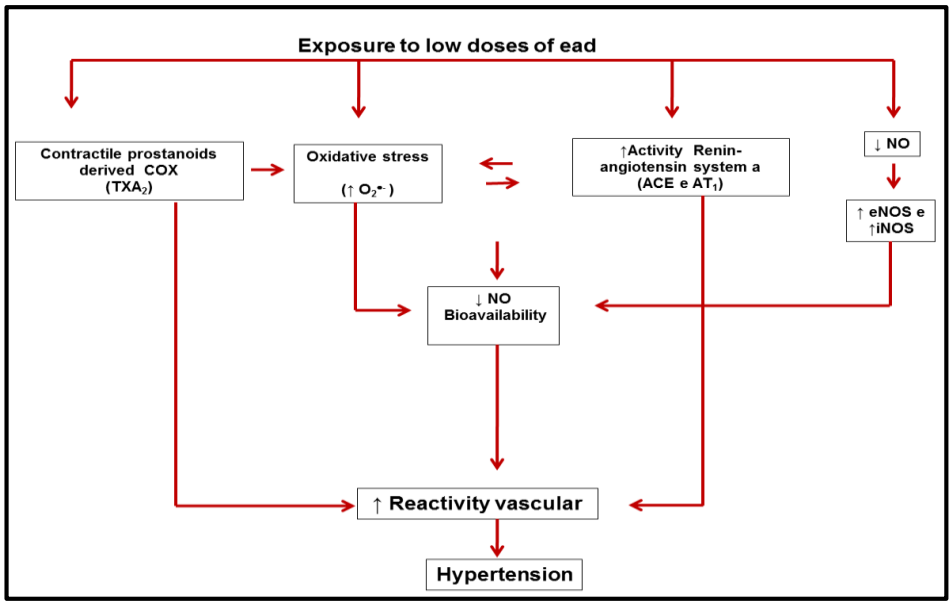

Figure 1: Representing the endothelial pathways involved in the effect of lead on the aorta artery of rats exposed to low doses of lead acetate (Silveira et al., 2010).

In other studies performed in our laboratory[26,44] the animals were exposed for 7 days at low doses (via intramuscular injections) of lead. After this period, a blood concentration of lead of 9.98 ± 1.70 µg/dL was observed in exposed animals. The functional and biochemical analyzes of these studies showed a reduction in the contractile response to phenylephrine and greater bioavailability of NO in aortic rings.[44] They also observed increased free radical production, potassium channel activation, and increased Na^+/K^+ -ATPase activity.[26] The authors of these studies suggest that increased NO and activation of potassium channels and sodium pump may reduce vascular tone in the early stages of exposure to lead by counteracting the vasoconstricting actions of free radicals.

On the other hand, Silveira et al,[27] studied the effects of lead 30 days after daily exposure (intramuscular injections) at low doses of this metal. After this period the exposed rats had a blood concentration of 12 ± 1.34 µg/dL. In this study, there was an increase in systolic blood pressure associated to functional and biochemical alterations analyzed in aortic rings of experimental animals. These authors propose that the increase in vascular reactivity can be attributed to the reduction in NO bioavailability caused by increased production of reactive oxygen species via NAD(P)H oxidase and also to the lower negative endothelial modulation, involving greater participation of the superoxide anion, of contractile prostanoids derived from COX, especially TXA_2 and participation of the renin-angiotensin system in this response. The functional results of this study were confirmed by some biochemical findings that showed an increase in the protein expression of the eNOS and iNOS isoforms and the AT_1 receptor. The main results of this study are summarized in figure (2) below.

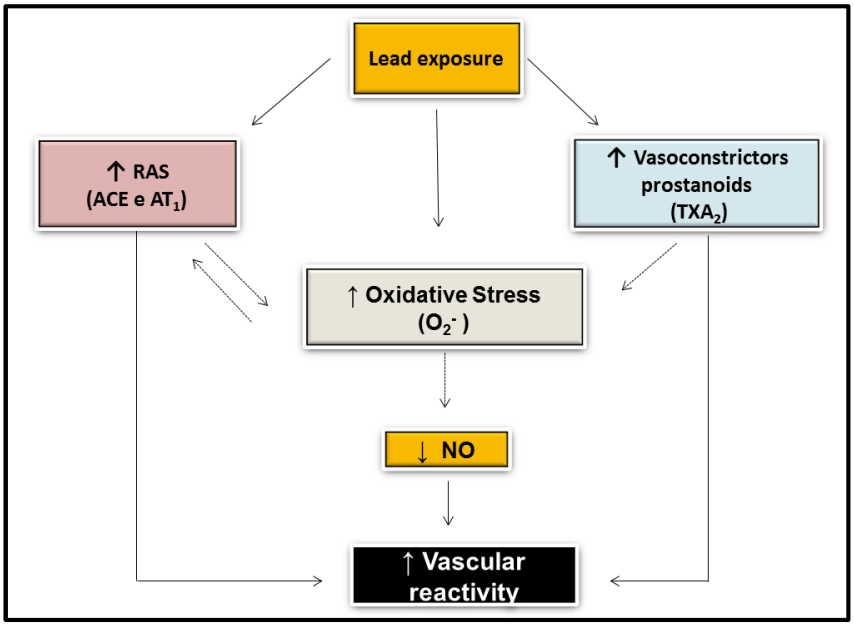

Figure 2: Representation of the endothelial pathways involved in the effect of lead on the rat aorta artery (Silveira et al., 2014).

Finally, Nunes et al,[45] investigated the effects of lead on the vascular reactivity of rat aortic arteries after 30 days of daily exposure to 100 ppm of lead in drinking water. The blood concentration of the animals exposed to lead was 8.4 µg/dL ± 1.1 µg/dL. The findings of this research revealed an increase in the production of superoxide anion (O_2^-) by NAD(P)H oxidase triggering a compensatory increase

in the activity of the enzyme superoxide dismutase (SOD). According to the authors, the increase in the activity of this enzyme increased the production of hydrogen peroxide (H_2O_2), which was responsible for the decrease in vascular reactivity. Figure 3 illustrates the main findings of this study.

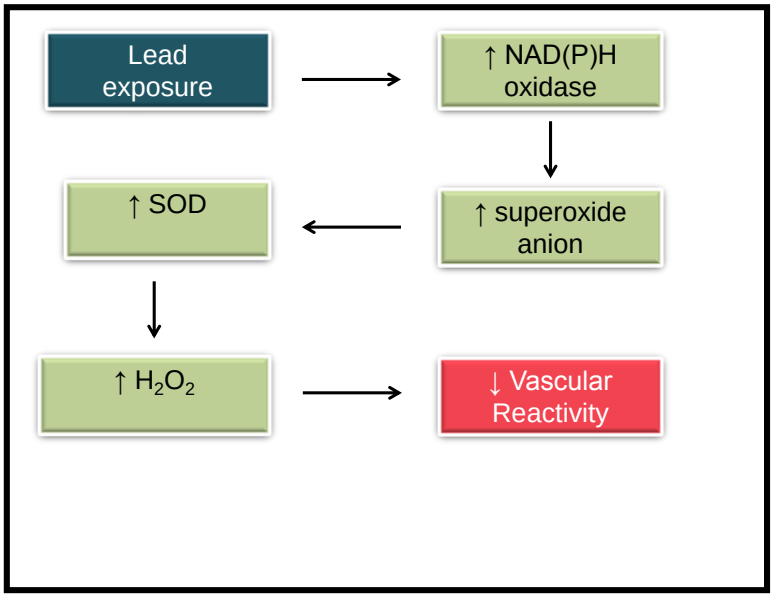

Figure 3: Representation of the main endothelial pathways in aorta after rings 30 days exposure to 100 ppm of lead acetate in drinking water (Nunes et al., 2015).

Analyzing the main findings found in the researches of Silveira et al,[27,43] Fiorim et al.,[26,44] and Nunes et al.,[45] we can observe that the deleterious effects of lead in the vascular reactivity of conductance vessels are dependent of time of exposure and also the way of exposure. This difference is clearly demonstrated in the results that showed increase[27,44] and reduction of vascular reactivity.[26,44, 45]

Conclusion

The studies presented in this review showed that lead promotes vascular changes resulting in increased blood pressure. It should be noted that these alterations are present in studies performed in both humans and experimental animals. It is known that cardiovascular diseases represent one of the main causes of death and morbidity in Brazil and in other countries. Therefore, we ratify the need to alert the toxicological surveillance agencies of the levels of lead exposure considered safe for individuals exposed to occupational and environmental contamination of this metal. In addition, it is important to include lead as a risk factor for the development of various cardiovascular diseases.

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REVIEW ARTICLE

Cardiac and blood pressure effects of lead exposure

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Keywords

Lead; Heart; Blood pressure

Abstract

Objective: To construct a review on cardiac effects and blood pressure of lead exposure. **Method**: This is a structured narrative review in three distinct phases: 1) elaboration of the guiding question: "What are the cardiac and blood pressure effects of lead exposure?"; 2) Sampling in the literature and selection of studies; 3) Critical analysis of selected studies. **Results**: several aspects related to cardiac effects and blood pressure of lead exposure were obtained, among them: arterial hypertension, autonomic dysregulation, dysregulation of myocardial contractility, increase in ventricular overload, increase in afterload and of the pulse pressure. Furthermore, the evidence is suggestive of an association between exposure to lead and mortality from cardiovascular causes, particularly related to ischemic heart disease. **Conclusion**: researchers on the subject warn that exposure to lead is reasoned as a cardiovascular risk factor.

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Introduction

Lead is a toxic metal and an environmental pollutant used in the manufacture of batteries, paints, ceramics, crystals, cables, ammunition and high-tech products, such as nuclear reactor protectors and thin plates of electronic components.[1]

Although several countries adopt measures to reduce the emission of lead, environmental contamination by this metal still remains a public health problem.[2] The World Health Organization (WHO) estimates that 140,000 people die every year, due to contamination by this metal, in addition to causing 600,000 cases of intellectual loss in children.[2]

Several studies have documented the adverse effects of lead exposure in the adult population and in children.[3-5] Young children are particularly vulnerable to the toxic and, in some cases, permanent effects of lead, especially by affecting the nervous system.[6] Studies indicate an association between blood lead concentration and development of hypertension, gastrointestinal disorders, as well as renal and cardiovascular dysfunctions.[1,6]

Considering the toxic potential of lead, this article seeks to compile information from the scientific literature and to support the construction of a reference on cardiac toxicity and the effects on blood pressure on exposure to this metal.

Method

This is a narrative review related to cardiac toxicity and the effects on blood pressure of lead exposure. We chose this type of literature review that allows the incorporation of evidence for convenience, for an expertise in the theme, in order to build a body of knowledge about a certain topic of scientific relevance.

The review process was systematized in three distinct phases, the first of which was the elaboration of the guiding question: "What are the cardiac effects and blood pressure of lead exposure?". The second phase corresponded to sampling in the literature, which sought to include the largest possible variety of identified products and ensure the variety and breadth of results.

In this sense, electronic selection was performed in the databases of LILACS (Latin American and Caribbean Literature) and MEDLINE (National Library of Medicine, USA). The electronic search was performed through the following combinations of Descriptors in Health Sciences (DeCS): "lead; toxicity; heart; Arterial pressure" and was based on the adoption of the following inclusion criteria: the indexing of studies in the respective databases in Portuguese, English and Spanish. Exclusion criteria were defined as: productions without availability of text in full or with a central theme of the study, unrelated to the topic of cardiac toxicity and effects on blood pressure in lead exposure.

The third phase of this review consisted of a critical analysis of the selected studies. The decision to include or reject the studies was based on the reading of the titles of the selected studies, followed by the critical analysis of the abstracts, and the studies with a central theme unrelated to the theme proposed for the review were rejected. In a second analysis, we verified the content in its entirety, which was guided by the thematic analysis technique to identify the central ideas presented.

Results / Discussion

In order to inform and contribute to analyzes and debates about the effects of exposure to lead, heart and blood pressure, the contents that make up the review were stratified in the following categories.

- Exposure to lead and hypertension

Population studies of the cardiovascular effects of lead are focused on the development of arterial hypertension while studies with experimental animals seek to elucidate the mechanisms involved in cardiovascular changes.[4,7-12]

Several clinical and epidemiological studies point to an association between exposure to lead and high blood pressure. However, only recently has it been shown that blood lead concentration below the limits considered safe for human health,[13,14] or exposure to a single dose of metal,[15] are able to raise the systolic blood pressure of experimental animals.

It is believed that the pathogenesis of lead toxicity in the development of hypertension is multifactorial, as: alter calcium homeostasis,[9,14,16] promote sympathetic hyperactivity,[14,17] induce increased renin-angiotensin system activity[15,18] to depress the antioxidant reserves of the organism and/or increase the production of reactive oxygen species (ROS), resulting in oxidative stress,[7,19,20] alter the vascular response to vasoactive agents,[13,21] promote endothelial damage, reduce bioavailability of nitric oxide and increase endothelin levels[11,22] besides inducing renal damage.[23]

- Exposure to lead and autonomic deregulation

Autonomic imbalance, characterized by hyperactivity of the sympathetic system and hypoactivity of the parasympathetic system, is associated with several pathological conditions that may favor the onset or aggravate cardiovascular diseases.[24-28] Some clinical and animal studies have focused on the Sympathetic system as a possible mediator of hypertension and cardiovascular diseases induced by lead exposure.

GUMP et al,[25] studied the cardiovascular response to acute stress in children exposed to low prenatal concentrations of lead and to low concentrations of this metal during childhood. These authors showed that the highest blood concentrations of lead are associated with higher systolic pressures and increased peripheral vascular resistance and, consequently, increased cardiac overload. Moreover, the blood concentration of lead was associated with a reduction in systolic volume and cardiac output, which were associated with a reduction in cardiac autonomic dysregulation.[26]

In adults, PARK and co-workers have shown that chronically exposed people may be more susceptible to cardiac autonomic dysfunction.[27,28] In experimental animals, sympathetic hyperactivity and its inotropic and chronotropic consequences in lead exposure are well documented.[9,14,17] Elevation of plasma norepinephrine and reduction of β-adrenergic receptor density are the two best mechanisms reported in interference in the autonomic regulation of lead exposure.

- Exposure to lead and elevation of pulse pressure

Chronic exposure to lead is associated with increased pulse pressure, a marker of arterial stiffness, and an indicator of cardiovascular disease. ZANGH et al.[29] studied 619 participants of the Normative Aging Study in the United States of America and demonstrated that H63D gene polymorphism of hemochromatosis (which may alter lead deposition and hence its cardiotoxic effect) increases susceptibility to deleterious effects of Lead in the pulse pressure. The increase of the pulse pressure is attributed to progressive arterial stiffness and consequent alteration in vascular structure and function with degradation of elastin, increase of collagen, calcification and atherosclerosis. These effects are made

possible by pro-oxidative or pro-inflammatory mechanisms that occur in lead exposure, since lead induces oxidative stress and this can promote direct damage in different organs and systems, including the heart itself.[30] The mechanisms by which Lead induces oxidative stress include lipid peroxidation in membranes, damage to the DNA and antioxidant system of the organism resulting in greater generation and/or availability of free radicals.[7,21,31]

- Exposure to lead and disturbances in myocardial contractility

Vassallo et al.[32] studied isolated right ventricle strips submitted to acute lead exposure and recorded reduction of isometric strength and indicated lead as a risk factor capable of altering cardiac function. Later, Fioresi et al.[9] investigated the acute effects of lead in the isometric contraction of isolated papillary muscles of the left ventricle of rats and demonstrated that the increase in ventricular pressure induced by acute exposure to lead has, besides vascular involvement, direct changes in myocardial contractility.

Fioresi et al.[14] showed that a blood concentration of lead, below the limits considered safe, results in an increase in blood pressure, HR and left ventricular inotropism, in addition to promoting changes in the calcium cycle of the cardiomyocyte, which may contribute to the deleterious effects of this metal on the heart.

Figure 1 shows the mechanisms by which lead, in the treatment model used by Fioresi et al,[14] alters the calcium cycle in the cardiomyocyte: there is a greater influx of transarcolemal calcium, but this higher influx does not result in positive inotropism, since the sarcoplasmic reticulum calcium pump (SERCA 2) is desensitized and the sodium-calcium exchanger (NCX) promotes the extrusion of these ions from the cell.

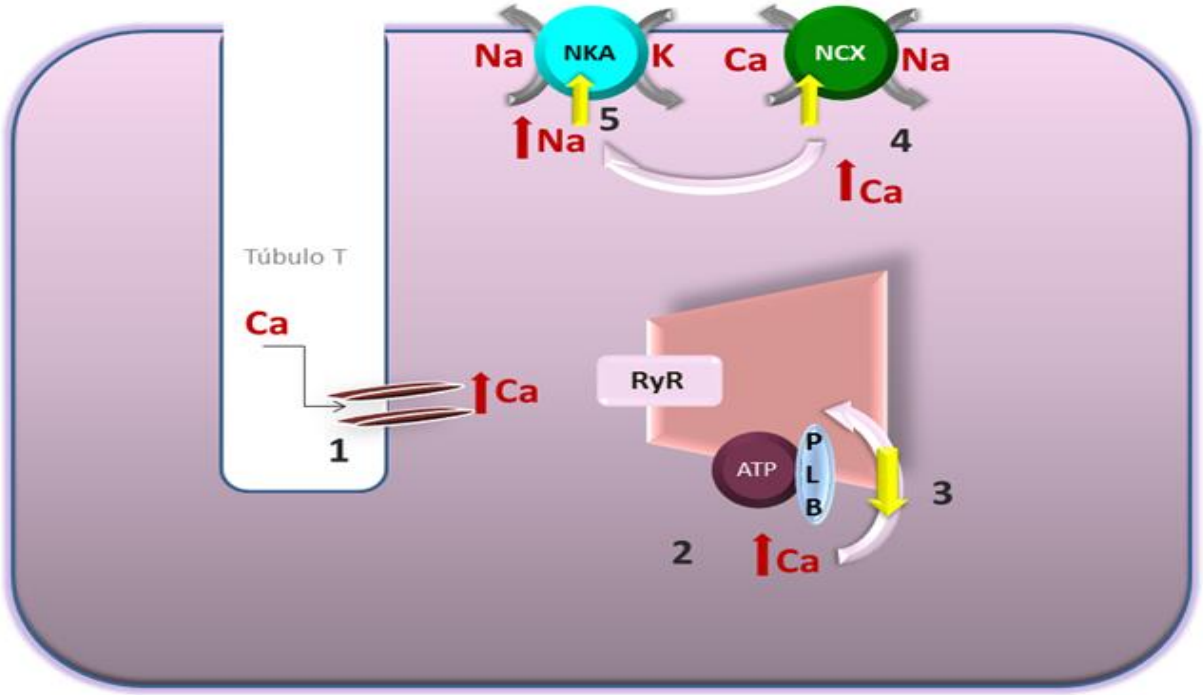

Figure 1: Mechanism proposed by which exposure to lead changes the calcium cycle in the cardiomyocyte. 1: Lead promotes greater influx of transarcolemal calcium; 2: There is an increase in [Ca] i; 3: There is desensitisation of SERCA 2 and less calcium reuptake; 4: Consequently, the increase in [Ca]i activates NCX to remove cytosolic calcium; 5: Increased NCX activity results in an increase in [Na]i, which in turn activates NKA.

- Exposure to lead and cardiovascular mortality

Several studies associate the blood concentration of lead to mortality. Weisskopf et al,[33] studied 868 men participating in the Normative Aging Study in the United States of America and found an association between lead bone content and cardiovascular mortality in the chronically exposed population at low blood concentrations of this metal. This association between lead exposure and mortality due to cardiovascular causes is particularly related to ischemic heart disease.[34] Although cardiac ischemic disease is multifactorial, exposure to lead may represent a risk factor that contributes to this outcome.[34]

There are several deleterious cardiovascular effects triggered by exposure to lead which, in combination, may lead to increased cardiovascular mortality.[4] Among these effects are: interference in cardiac contractility;[9,14,32] increase in vascular tone and peripheral resistance;[19] stimulation of the renin-angiotensin system;[15,18] reduction in the availability of nitric oxide and increased oxidative stress;[13,35] interference in the cardiac autonomic control.[36]

Conclusion

Lead has toxic effects on the heart and exposure to this metal may be considered a cardiovascular risk factor, since several studies point to a causal relationship between this exposure and the development of hypertension.

There is sufficient evidence that chronic exposure to lead has deleterious cardiac effects by affecting autonomic regulation and promoting ventricular overload, by increasing pressure afterload and pulse pressure. Furthermore, the evidence is suggestive of an association between exposure to lead and mortality from cardiovascular causes, particularly related to ischemic heart disease.

Although there is a need for further research, especially clinical and epidemiological studies, to clarify the effects and mechanisms involved in lead cardiotoxicity, it is essential for the responsible public agencies to reevaluate the safe exposure values and that the investigation of exposure to this metal to be routinely included in the cardiovascular research, mainly in workers occupationally exposed to lead.

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