Marked elevation of myocardial trace elements in idiopathic dilated cardiomyopathy compared with secondary cardiac dysfunction

Andrea Frustaci, Nicola Magnavita, Cristina Chimenti, Marina Caldarulo, Enrico Sabbioni, Romano Pietra, Carlo Cellini, Gian Federico Possati, and Attilio Maseri

This information is current as of March 5, 2011

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://content.onlinejacc.org/cgi/content/full/33/6/1578

JACC

JOURNAL *of the* AMERICAN COLLEGE *of* CARDIOLOGY

Marked Elevation of Myocardial Trace Elements in Idiopathic Dilated Cardiomyopathy Compared With Secondary Cardiac Dysfunction

Andrea Frustaci, MD,* Nicola Magnavita, MD,† Cristina Chimenti, MD,* Marina Caldarulo, MD,†
Enrico Sabbioni, PHD,‡ Romano Pietra, PHD,‡ Carlo Cellini, MD,§ Gian Federico Possati, MD,§
Attilio Maseri, MD*

Rome, Italy

OBJECTIVES	We sought to investigate the possible pathogenetic role of myocardial trace elements (TE) in patients with various forms of cardiac failure.
BACKGROUND	Both myocardial TE accumulation and deficiency have been associated with the development of heart failure indistinguishable from an idiopathic dilated cardiomyopathy.
METHODS	Myocardial and muscular content of 32 TE has been assessed in biopsy samples of 13 patients (pts) with clinical, hemodynamic and histologic diagnosis of idiopathic dilated cardiomyopathy (IDCM), all without past or current exposure to TE. One muscular and one left ventricular (LV) endomyocardial specimen from each patient, drawn with metal contamination-free technique, were analyzed by neutron activation analysis and compared with 1) similar surgical samples from patients with valvular (12 pts) and ischemic (13 pts) heart disease comparable for age and degree of LV dysfunction; 2) papillary and skeletal muscle surgical biopsies from 10 pts with mitral stenosis and normal LV function, and 3) LV endomyocardial biopsies from four normal subjects.
RESULTS	A large increase (>10,000 times for mercury and antimony) of TE concentration has been observed in myocardial but not in muscular samples in all pts with IDCM. Patients with secondary cardiac dysfunction had mild increase (≤5 times) of myocardial TE and normal muscular TE. In particular, in pts with IDCM mean mercury concentration was 22,000 times (178,400 ng/g vs. 8 ng/g), antimony 12,000 times (19,260 ng/g vs. 1.5 ng/g), gold 11 times (26 ng/g vs. 2.3 ng/g), chromium 13 times (2,300 ng/g vs. 177 ng/g) and cobalt 4 times (86,5 ng/g vs. 20 ng/g) higher than in control subjects.
CONCLUSIONS	A large, significant increase of myocardial TE is present in IDCM but not in secondary cardiac dysfunction. The increased concentration of TE in pts with IDCM may adversely affect mitochondrial activity and myocardial metabolism and worsen cellular function. (J Am Coll Cardiol 1999;33:1578–83) © 1999 by the American College of Cardiology

Idiopathic dilated cardiomyopathy (IDCM) is, by definition, a disease characterized by dilation and impaired contraction of the left or both ventricles. Its etiology is still unknown and the pathogenetic mechanism debated, although a viral and/or immune, genetic/familial or toxic mechanism has been suggested (1–8).

Trace elements (TE) are known to have a key role in myocardial metabolism and both TE accumulation (cobalt, arsenic) and deficiency (selenium, i.e., Keshan disease) may be responsible for a dilated cardiomyopathy indistinguishable from an idiopathic form (9,10). It has been documented that even a Coxsackie viral infection can cause a great TE accumulation in the mouse heart (11,12).

To investigate the possible pathogenetic role of TE in IDCM, 32 TE were assessed by neutron activation analysis in left ventricular (LV) endomyocardial and muscular biopsy specimens from patients with IDCM and specific forms of cardiac dysfunction.

METHODS

Patient population. Thirteen patients (9 male, 4 female, mean age 50.9 ± 10.1 years) with IDCM (group A) were included in the study (Table 1). The patients were admitted to our institution because of dyspnea (New York Heart Association class II–IV) and palpitation. No patients had hypertension, drug or alcohol abuse, ischemic heart disease or systemic disorders. All patients underwent noninvasive

(electrocardiography, two-dimensional echocardiography and Holter monitoring) and invasive (cardiac catheterization, coronary arteriography and left ventricular endomyocardial biopsy) cardiac studies. Endomyocardial biopsies were performed in the septal–apical region of left ventricle, which was approached by a 7-F (501-613A Cordis) long sheet and identified on an X-ray view using flashing of contrast medium (iohexol, Omnipaque, Nycomed). Three to four left ventricular samples were drawn, processed for histology and electron microscopy and read by a pathologist blinded to the clinical data. Specifically, the tissue specimens for light microscopy were fixed in 10% buffered formaline, and embedded in paraffin wax; 5-μm thick sections were cut and stained with hematoxylin–eosin, Miller's elastic Van Gieson and Masson's trichrome. For electron microscopy all samples of myocardial tissue were fixed in a solution of 2% glutaraldehyde in a 0.1 mol/L phosphate buffer, at pH 7.3 and embedded in an Epon resin following a standard schedule. Ultrathin sections were stained with uranyl acetate and lead citrate.

Morphometry, using a grid and point and counting system (13), was applied on histologic slides to assess the extent of myocardial fibrosis, and its prevalence was correlated with the degree of impairment of cardiac function (LV ejection fraction) and the myocardial content of TE.

A second correlative study was also performed on the myocardial content of the TE and the arrhythmic profile of each patient (Lown class) based on the results of Holter recordings (3 to 5 each patient) and/or electrocardiographic findings during hospital admissions. Needle muscle biopsies of vastus lateralis muscle were performed using a Bard Biopsy instrument with a 14-gauge needle as described (14) in patients with IDCM. Environmental exposure to heavy metals and toxic TE was assessed by means of a questionnaire.

Control samples for histology, morphometry and TE analysis were:

Group B: Left ventricular endomyocardial and thoracic muscle biopsy samples from 12 patients (eight male, four female mean age 53 ± 10 years) with valvular heart disease (mitral regurgitation in four patients aortic stenosis in three patients, aortic regurgitation in two patients, aortic stenosis and regurgitation in three patients) left ventricular dilation (left ventricular end-diastolic diameter [LVEDD] = 69.5 ± 7.48 mm) and depressed LV function (left ventricular ejection fraction [LVEF] = 30 ± 6.3%) obtained during the surgical replacement of the valve; left ventricular endomyocardial and thoracic muscle biopsies from 13 patients (10 male, three female, mean age 58.8 ± 9.7 years) with ischemic heart disease, LV dilation (LVEDD = 67.3 ± 4.8 mm) and LV dysfunction (LVEF = 33 ± 4%) taken at the time of coronary artery bypass surgery.

Group C. Papillary and thoracic muscular biopsies from 10 patients (five male, five female mean age 55.2 ± 8.6 years) with mitral stenosis and normal LV dimen-

Table 1. Data on 13 Patients With Idiopathic Dilated Cardiomyopathy

Pts	Age/Gender	NYHA Class	LVEDD (mm)	LVEF	CI (liters/min/m²)	Fibrosis	Ventricular Arrhythmias (Lown Class)	Hg (ng/g) in My	Sb (ng/g) in My
1	31/M	III	75	25%	2.0	3.1%	4b (nsVT)	108,000	18,200
2	41/F	I	70	35%	2.3	7.5%	3	52,700	3,600
3	59/M	IV	78	18%	1.8	3.4%	4b (nsVT)	160,000	32,500
4	54/M	I	68	40%	2.4	6%	2	49,000	6,500
5	51/M	II	70	30%	2.1	5.5%	3	91,800	29,900
6	43/M	II	66	32%	2.3	9.5%	3	42,200	11,000
7	54/M	III	74	20%	1.9	3%	2	9,300	2,000
8	65/M	III	80	25%	2.0	6.5%	4b (nsVT)	176,700	36,900
9	62/F	II	71	39%	2.5	3.5%	3	44,800	4,500
10	59/F	III	76	25%	2.1	5.75%	4b (sVT)	865,000	98,800
11	55/F	III	73	22%	2.0	4.5%	4b (sVT)	409,000	49,500
12	37/M	IV	80	18%	1.7	3%	4b (nsVT)	225,000	37,200
13	41/M	I	65	42%	2.6	5.5%	3	86,000	5,500

CI = cardiac index; EDD = end-diastolic diameter; EF = ejection fraction; Hg = mercury; LV = left ventricular; My = myocardium; ns = nonsustained; NYHA = New York Heart Association; Pts = patients; s = sustained; VT = ventricular tachycardia.

sion (LVEDD = 48.2 ± 2.6 mm) and function (LVEF = 56.1 ± 4.4%) undergoing mitral valve replacement (control subjects).

Group D. Normal LV endomyocardial biopsies (section of specimens with normal histologic findings) from four patients (two male, two female, mean age 54 ± 4.5 years) who underwent a diagnostic cardiac catheterization with ventricular and coronary angiography because of chest pain, which showed normal coronary arteries, LV volumes and LV function. Moreover, in order that a uniform procedure was followed, biopsy specimens were taken from patients and control subjects using a Bipal Cordis bioptome.

Trace elements assessment. One ventricular biopsy specimen (weight range: 1.5 to 2.8 mg/wet weight) was processed to determine the levels of TE by neutron activation analysis (15). The following elements were analyzed: silver (Ag), arsenic (As), gold, barium, calcium (CA), cadmium, cerium, cobalt, chromium, cesium, eruopium, iron, hafnium, mercury (Hg), iridium, lanthanum, lutetium, molibdenum, nickel, rubidium, antimony (Sb), scandium, selenium, samarium, tin, strontium, tantalum, terbium, thorium, uranium, ytterbium, zinc and zirconium.

When metallic surgical instruments are used to collect human tissue, metal contamination may occur, thus making it difficult to assess accurately the levels of ultratrace metal elements (16). To reduce this bias as much as possible, surgical instruments made from a stainless-steel core covered by a film of titanium nitride (a very hard compound with a high chemical stability and very good wear resistance) were used. Samples were kept frozen until irradiation.

The observed values were compared with control samples and with data from the literature (17–19).

Statistical analysis. Data were analyzed by means of SPSS/PC+ (Cary, North Carolina). Continuous data were summarized as mean ± SD. The difference between two groups was tested by Mann-Whitney *U* test. The relation between continuous variables was assessed by the method of the least squares. A two-tailed p value < 0.05 was considered significant.

RESULTS

No cases of occupational exposure to TE were observed, not did any patients or control subjects come from heavily polluted geographic areas.

Clinical study. Echocardiography showed an increase of LVEDD (72.7 ± 4.9 mm) and a significant impairment of left ventricular function (LVEF = 28.5% ± 8.4%). No significant valvular abnormalities were present.

Holter monitoring revealed in all patients frequent ventricular ectopic beats with some couples and triplets and in six cases phases of nonsustained or sustained ventricular tachycardia (Lown class 4b) (Table 1). We performed a

Holter monitoring also in control subjects with secondary cardiac dysfunction, which failed to show repetitive ventricular ectopic beats (Lown ≤3). Cardiac catheterization and left ventriculography confirmed the compromised global contractility with reduction of cardiac index and elevation of left ventricular filling pressure (Table 1). Coronary angiography showed a normal arteriogram in every case.

Histology of left ventricular biopsy fragments from each patient ruled out specific heart muscle diseases such as myocarditis, and storage or infiltrative heart muscle diseases, while showing signs of hypertrophy with attenuation and degenerative changes of myocardial fibers.

Electron microscopy showed degenerative changes to consist of loss of contractile elements, the presence of myelin bodies and the vacuolization of mitochondria with fragmentation of mitochondrial cristae.

Myocardial and muscle TE concentration. In the majority of cases, in both patients and control subjects, myocardial concentrations of Ca, cadmium, hafnium, iridium, lutetium, molibdenum, samarium, tin, strontium, tantalum, terbium, thorium, uranium, ytterbium and zirconium appeared to be below the lower analytical determination limit. In control subjects, concentrations of cerium, cesium, europium, nickel and scandium were below the determination limit. Mean concentration values of the remaining 13 elements in patients (groups A and B) and controls (group C) are shown in Table 2. The mean concentration of these TE was in the range of normal reference values (18) both in control subjects (group C) and in the four normal subjects (group D).

A severe increase in Hg and Sb was observed in IDCM patients (patients/control subjects ratio >10,000). In addition, Ag, As, gold, chromium, lanthanum and zinc levels were 10 to 250 times higher in patients than in control subjects. Trace elements concentrations in papillary muscle biopsies were within the normal range of variation.

In IDCM patients the mean concentrations were 178,400 ng/g for Hg, 19,260 ng/g for Sb and 625 ng/g for As, whereas corresponding values in normal control subjects were 8 ng/g, 1.5 ng/g and 2.5 ng/g respectively. In patients with specific forms of cardiac dysfunction the mean concentration of Hg was 30 ng/g in patients with valvular heart disease and 23 ng/g in patients with ischemic heart disease, of Sb was 6 ng/g and 6.5 ng/g and of As was 9.3 and 10.3 respectively (Table 2). Corresponding reference interval values in published reports were 5 to 480 ng/g for Hg, 2 to 35 ng/g for Sb and 4.4 to 14 ng/g for As in myocardial tissue (18).

The values given are well above the normal range. Moreover, the Hg soft tissue body burden of Hg in a reference man weighing 70 kg is estimated to be 13 mg, and the total body burden of Sb is about 1 mg (20). In IDCM patients a simple calculation reveals up to 17.8 mg/100 g of heart tissue for Hg, and 1.9 mg/100 g for Sb, thus showing that these TE are stored abnormally in myocardial tissue.

Table 2. Mean Myocardial Trace Elements Concentration (ng/g) in Patients With Idiopathic Dilated Cardiomyopathy (Group A), Secondary Forms of Cardiac Dysfunction (Group B), Control Subjects (Group C) and Normal Subjects (Group D) as Determined by Neutron Activation Analysis

Element	Normal Range	Group A	Group B Valvular	Group B Ischemic	Group C	Group D	Ratio A/C
Ag	3.3–260	116	17	13	4	7	29
As	4.4–14	625	9.3	10.3	2.5	4	250
Au	0.045	26	7	11	2.3	3.2	11.3
Ba	7.6–2,020	7,360	6,200	5,300	1,500	1,250	4.9
Co	10–210	86.5	100	89	20	15	4.3
Cr	11–480	2,300	630	720	177	100	13
Fe	36,000–180,000	106,700	130,200	148,700	39,000	34,000	2.7
Hg	5–480	178,400	30	23	8	6	22,300
La	1	43.3	5	3.5	1.2	0.9	36
Rb	1,200–8,100	18,700	3,200	3,565	3,880	3,200	4.8
Sb	2–35	19,260	6	6.5	1.5	1.1	12,840
Se	49–5,000	383	270	230	250	220	1.5
Zn	17,800–113,000	128,000	16,000	21,000	9,000	7,500	14.2

Ag = silver; As = arsenic; Au = gold; Ba = barium; Co = cobalt; Cr = chromium; Fe = iron; Hg = mercury; La = lanthanum; Rb = rubidium; Sb = antimony; Se = selenium; Zn = zinc.

No correlation was found between the concentrations of each TE and the age of the patient. The correlation coefficients between TE and age did not reach the statistical level of significance (correlation coefficients for Hg = 0.25, $p = 0.42$; for Sb = 0.26, $p = 0.39$).

No differences were observed in the levels of myocardial TE in male and female subjects ($p = 0.44$ for Hg; $p = 0.76$ for Sb).

The degree of myocardial fibrosis, assessed by microscopic examination of histologic fields, was mild to moderate ($\leq 9.5\%$) and did not appear to be correlated with Hg or Sb concentrations (correlation coefficients for Hg = -0.03, $p = 0.92$; for Sb = -0.05, $p = 0.87$).

Patients with higher concentrations of myocardial TE appeared to have a more pronounced degree of LV impairment and electrical instability (see Table 1). Those with the most pronounced degree of LV impairment (LVEF <0.30) had higher average concentrations of Hg (279 vs. 61 ng/g, $p = 0.03$) and Sb (39.3 vs. 10.2 ng/g, $p = 0.04$) than those with partially preserved myocardial function (LVEF, between 0.30 and 0.49); patients with sustained and nonsustained ventricular tachycardia showed higher concentrations of TE than those without (Hg 324 vs. 54 ng/g, $p = 0.0027$; Sb 45.5 vs. 9,0 ng/g, $p = 0.0043$).

Skeletal muscle concentrations of the 32 TE examined were in the normal range in all patients and control subjects. In particular muscle concentration of Hg and Sb were <150 ng/g and <193 ng/g respectively (18).

DISCUSSION

The most relevant result of our study is a large increase of the myocardial content of some TE in patients with IDCM not documented in patients with specific heart muscle disease presenting comparable degree of left ventricular

dysfunction. This increase has an obvious statistical significance and its biologic significance needs to be evaluated.

Consideration on TE assessment. Most of the data reported in published reports on TE in human tissues are of limited value in the assessment of their toxicologic impact: this is due not only to individual biologic variations, but also to errors caused by analytic inconsistencies (21). Patent discrepancies can be observed among studies conducted by spectrographic and neutron activation methods. Neutron activation analysis has been shown to be the most advantageous method for quantitative determination of TE in human tissues owning to its high level of precision, high specificity and high accuracy (22). Particular attention has to be paid to preanalytic factors, such as ethnic variations, sampling, sample handling and storage.

Preanalytic factors on TE assessment. The range of values that we considered as normal for myocardial and muscular content of TE is argued from a review (18) of international published data on the elemental composition of human tissues of healthy, adult individuals from populations of different ethnicity. We can therefore postulate that these reference values were appropriate also for our population.

Moreover in our study both patients and control subjects were of the same geographic area and ethnicity (white Italian people) making unlikely that difference on TE concentration might be due to different genetic patterns.

Loss of water from small myocardial samples during analysis could lead to overestimation of the intramyocardial content of TE; evaporation could be as high as 50% of total weight. Data interpretation should, therefore, be cautious and doubled values should be regarded as normal. It would also take into account the biologic sources of variation. In

autopsy studies, postmortem process and contamination of tissues by residual blood could lead to relatively high errors for several TE (23); there is, however, no fear of this in our study.

Gender has not been proved to play a significant role in the distribution of TE (19), and, in agreement with the published data our study showed no significant gender differences in either IDCM patients or control subjects.

The body burden of most elements seems to be influenced significantly by age. Most TE are very low at birth and build up rapidly thereafter (24–25); after the age of three months, however, such differences tend to disappear and, in some studies, no significant differences associated with age have been obtained (19). The comparison of myocardial samples from young people (which we used as our control subjects) and adults may show slight differences in the levels of TE; an increase of three to four orders of magnitude, however, cannot depend on physiologic aging.

Another factor to consider is the anatomic distribution of TE. Differences in the levels of TE in different anatomic regions of the heart have been reported in animals (26–28), but at present there is insufficient evidence to suggest that such a difference occurs in humans. No apparent differences were noted between the concentrations of TE in different parts of the ventricular myocardium (19).

Finally a direct or indirect effect of contrast medium on myocyte TE concentration can be taken into consideration. Indeed, surgical control samples showing normal TE values were obtained several days or weeks after catherization and angiography, whereas biopsy specimens of patients with IDCM were drawn right after the angiographic study. Nevertheless TE values observed in normal LV biopsies from four subjects undergoing an invasive study, including coronary and ventricular angiography, were found to be within normal limits. We can therefore reasonably rule out any effect, due either to TE contamination or to interference of iodine on the myocardial TE concentration.

In conclusion, the observed increase in the myocardial content of some TE is likely to reflect a pathologic phenomenon.

Side of myocardial TE increase. The increased concentrations of TE in the myocardium could depend on an increase of myocardial fibrous tissue, or an increase in endocellular concentrations of TE, or both. Morphometry, however, failed to show a correlation between the degree of myocardial fibrosis and the levels of TE. It seems, therefore, that myocardial accumulation of TE in IDCM should be mostly intracellular, which is in agreement with the extensive pathologic evidence that points to myocardial cell degeneration and dysfunction, rather than replacement of myocardiocytes by fibrous tissue, as the source of failure in IDCM.

Trace elements and ventricular arrhythmias. As far as the arrhythmic profile of our IDCM patients is concerned, a similar correlative trend was observed when comparing the severity of ventricular arrhythmias with myocardial concen-

trations of TE. Although the number of patients studied may not be representative, the incidence of ventricular tachycardia seems to be associated with higher values of TE (Table 1). In fact, in patients with Lown class 4b we found higher values of Ag and Sb than in patients with Lown class 2–3, and among these patients, No. 10 and No. 11, who showed episodes of sustained ventricular tachycardia on Holter monitoring, had the highest values. In patients with secondary forms of cardiac dysfunction and mild elevation of TE the Holter monitoring showed only a Lown class ≤3.

In summary, high increases of some TE in the myocardial tissue of patients with IDCM seem to correlate with the severity of cardiac impairment, as well as that of electrical instability.

Trace elements in IDCM compared with secondary cardiac dysfunction. In patients with valvular and ischemic cardiomyopathies having comparable degree of left ventricular dysfunction, only mild (≤5 times normal control subjects) increase of TE was documented. This point together with the absence of signs and/or symptoms of TE intoxication and the normal TE values observed on skeletal muscle biopsies suggest that myocardial TE accumulation is specifically correlated with the pathogenesis of IDCM itself.

Possible mechanism of TE accumulation in IDCM. Actually we are unable to explain its mechanism, as dilated cardiomyopathy remains an idiopathic entity. The more reliable, although unconfirmed, pathogenetic hypothesis for IDCM, is that of a virus-induced disease. It has been documented that a common viral (Coxsackie virus) infection can change TE target organ distribution in mice with greatly increased accumulation of nickel (11), cadmium and mercury (12) in the wall of the ventricular myocardium. We can speculate that a cardiac viral infection might induce an impairment of cellular biomembranes, which could, in turn, increase the input or reduce the output of certain TE, determining toxic intracellular concentrations.

Potential consequences of TE accumulation in IDCM. At present, we are unable to establish the toxic threshold levels of TE in the myocardium, since biopsy data on patients with toxic TE exposure are not available. The extremely high values of Hg and Sb found in our patients with IDCM makes it unlikely that there would be no adverse effect. Indeed, each of the TE increased in IDCM myocardial tissue may interfere with cellular activities. Particularly heavy metals (i.e., Hg, Sb, Ag) whose values were the most elevated, are known to induce the formation of oxygen free radicals in the affected tissues (29–31). Superoxide anions and radicals can, in turn, inhibit cardiac sodium pump and several other ion transporters of the plasma membrane (32). The final results may well be the idropic degeneration and the mitochondrial damage of myocardiocytes that are observed at histology and electron microscopy in IDCM.

Finally heavy metals can antagonize Ca^{++} at actin–

myosin junction in a concentration-dependent way, producing a progressive decline of sarcomere contraction and thus of myocyte function. On pharmacologic grounds, drugs such as the inotropic agents that work on increasing intracellular Ca^{++} may find the reason of their inefficacy in dilated cardiomyopathy.

Conclusions. The accumulation of some TE seems to be a constant finding in IDCM but not in specific cardiomyopathies. This abnormality is limited to the myocardium and correlates with the severity of both heart failure and electrical instability. However, the mechanisms of the accumulation of TE and its consequence on myocyte structure and function need to be further elucidated.

Address correspondence and reprint requests: Andrea Frustaci, MD, Department of Cardiology, Catholic University, Largo A. Gemelli 8, 00168 Rome, Italy.

REFERENCES

1. Report of the 1995 WHO/ISFC Task Force on the definition and classification of cardiomyopathies. Circulation 1996;93:841–2.
2. Caforio AL, Stewart JT, Bonifacio E, et al. Inappropriate major histocompatibility complex expression on cardiac tissue in dilated cardiomyopathy. Relevance for autoimmunity? J Autoimmun 1990;3:187–200.
3. Limas CJ, Limas C. Immune-mediated modulation of sarcoplasmic reticulum function in human dilated cardiomyopathy. Basic Res Cardiol 1992;87 Suppl 1:269–76.
4. Olsen EG. The pathogenesis of dilated cardiomyopathy. Postgrad Med J 1992;68 Suppl 1:S7–10.
5. Taha TH, Mazeika PK, Oakley CM, Maisch B. Cardiocytolytic antimyolemmal antibodies in dilated cardiomyopathy following presentation: observations in 7 patients. Int J Cardiol 1993;38:133–40.
6. Why HJ, Meany BT, Richardson PJ, et al. Clinical and prognostic significance of detection of enteroviral RNA in the myocardium of patients with myocarditis or dilated cardiomyopathy. Circulation 1994;89:2582–9.
7. Caforio AL, Keeling PJ, Zachara E, et al. Evidence from family studies for autoimmunity in dilated cardiomyopathy. Lancet 1994;344:773–7.
8. Michels VV, Moll PP, Miller FA, et al. The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. N Engl J Med 1992;326:77–82.
9. McCall D. Alcohol and the cardiovascular system. Curr Probl Cardiol 1987;12:1–414.
10. Reeves WC, Marcuard SP, Willis SE, Movahed A. Reversible cardiomyopathy due to selenium deficiency. J Parenter Enteral Nutr 1989;13:663–5.
11. Ilback NG, Fohlman J, Friman G. A common viral infection can change nickel target organ distribution. Toxicol Appl Pharmacol 1992;114:166–70.
12. Ilback NG, Lindh U, Fohlman J, Friman G. New aspects of murine Coxsackie B3 myocarditis—focus on heavy metals. Eur Heart J 1995;16:20–4.
13. Brandrup U, Olsen EGJ. Critical analysis of endomyocardial biopsies from patients suspected of having cardiomyopathy. Br Med J 1981;45:475–86.
14. Cotè AM, Jimenez L, Adelman LS, Munsat TL. Needle muscle biopsy with the automatic Biopty instrument. Neurology 1992;42:2212–3.
15. Nicolau G, Pietra R, Sabbioni E, Mosconi G, Cassina G, Seghizzi P. Multielement determination of metals in biological specimens of hard metal workers: a study carried out by Neutron Activation Analysis. J Trace Elem Electrolytes Health Dis 1987;1:73–7.
16. Pietra R, Sabbioni E, Brossa F, Gallorini M, Faruffini G, Fumagalli EM. Titanium nitride as a coating for surgical instruments used to collect human tissue for trace metal analysis. Analyst 1990;115:1025–8.
17. Aalbers TG, Houtman JPW, Makkink B. Trace-element concentrations in human autopsy tissue. Clin Chem 1987;32:2057–64.
18. Iyengar GV, Kollmer WE, Bowen HJM. The Elemental Composition of Human Tissues and Body Fluids. Weinheim, New York: Verlag Chemie, 1978;55–82.
19. Wester PO. Trace elements in heart tissue. Acta Med Scand 1965;Suppl 439:1–48.
20. Carson BL, Ellis HV III, McCann JL. Toxicology and Biological Monitoring of Metals in Humans. Chelsea (MI): Lewis, 1986:21–46.
21. Minoia C, Pietra R, Sabbioni E, et al. Trace element reference values in tissues from inhabitants of the European Community. III. The control of preanalytical factors in the biomonitoring of trace elements in biological fluids. Sci Total Environ 1992;120:63–79.
22. Salbu B, Steinnes E. Applications of nuclear analytical techniques in environmental research. Plenary lecture. Analyst 1992;117:243–9.
23. Aalbers TG, Houtman JPW. Relationships between trace elements and atherosclerosis. Sci Total Environ 1985;43:255–83.
24. Vuori E, Huunan-Seppala A, Kilpio JO. Biologically active metals in human tissues. I—The effect of age and sex on the concentration of copper in aorta, heart, kidney, liver, lung, pancreas and skeletal muscle. Scand J Work Environ Health 1978;4:167–75.
25. Vuori E, Huunan-Seppala A, Kilpio JO. Biologically active metals in human tissues. II—The effect of age on the concentration of cadmium in aorta, heart, kidney, liver, lung, pancreas and skeletal muscle. Scand J Work Environ Health 1979;5:16–22.
26. Webb J, Kirk KA, Niedermeier W, Griggs JH, Turner ME, James TN. Distribution of 8 trace metals in beef heart tissue. Bioinorg Chem 1976;5:253–9.
27. Webb J, Kirk KA, Niedermeier W, Griggs JH, Turner ME, James TN. Use of pattern recognition to classify beef cardiovascular tissues on the basis of their trace metal compositions. Bioinorg Chem 1976;5:261–6.
28. Webb J, Kirk KA, Niedermeier W, Griggs JH, Turner ME, James TN. Distribution of 9 trace metals in 17 anatomic sites of dog heart tissue and their classification using pattern recognition. Bioinorg Chem 1977;7:303–14.
29. Chevion M. Protection against free radical-induced and transition metal-mediated damage: the use of "pull" and "push" mechanisms. Free Radic Res Commun 1991;12/13:691–6.
30. Coudray C, Boucher F, Richard MJ, Arnaud J, De Leiris J, Favier A. Zinc deficiency, ethanol, and myocardial ischemia affect lipoperoxidation in rats. Biol Trace Elem Res 1991;30:103–18.
31. Tirmenstein MA, Plews PI, Walker CV, Woolery MD, Wey HE, Toraason MA. Antimony-induced oxidative stress and toxicity in cultured cardiac myocytes. Toxicol Appl Pharmacol 1995;130:41–7.
32. Xie ZJ, Wang YH, Askari A, Huang WH, Klaunig JE, Askari A. Studies on the specificity of the effects of oxygen metabolites on cardiac sodium pump. J Mol Cell Cardiol 1990;22:911–20.

Marked elevation of myocardial trace elements in idiopathic dilated cardiomyopathy compared with secondary cardiac dysfunction

Andrea Frustaci, Nicola Magnavita, Cristina Chimenti, Marina Caldarulo, Enrico Sabbioni, Romano Pietra, Carlo Cellini, Gian Federico Possati, and Attilio Maseri

This information is current as of March 5, 2011

Updated Information & Services	including high-resolution figures, can be found at: http://content.onlinejacc.org/cgi/content/full/33/6/1578
References	This article cites 28 articles, 5 of which you can access for free at: http://content.onlinejacc.org/cgi/content/full/33/6/1578#BIBL
Citations	This article has been cited by 4 HighWire-hosted articles: http://content.onlinejacc.org/cgi/content/full/33/6/1578#otherarticles
Rights & Permissions	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://content.onlinejacc.org/misc/permissions.dtl
Reprints	Information about ordering reprints can be found online: http://content.onlinejacc.org/misc/reprints.dtl