Cobalt Cardiomyopathy
A Critical Reappraisal in Light of a Recent Resurgence

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Abstract—Cobalt can cause a distinctive, rapidly progressive and reversible depression of cardiac systolic function, which is readily distinguished from other causes of cardiomyopathy. Patients present with the subacute onset of severe heart failure, which is accompanied by hypotension and cyanosis, pericardial effusion, low voltage on the electrocardiogram, marked elevation of serum enzymes, and lactic acidosis. They typically have a history of lethargy, anorexia, and weight loss in the months preceding the illness and exhibit other evidence of cobalt's effects on the body (eg, polycythemia and goiter). The course of cobalt-related cardiomyopathy may be progressive and fatal, but those who survive and cease exposure generally demonstrate complete resolution of symptoms and recovery of cardiac function. Patients presenting with rapid onset of cardiomyopathy, who also exhibit polycythemia, pericardial effusion, or goiter should be evaluated for cobalt exposure. Exposure can be confirmed by the measurement of cobalt in the serum, but serum levels of the ion are not reliably predictive of clinical cardiotoxicity. The clinical emergence of cobalt cardiomyopathy seems to require the coexistence of one or more cofactors, particularly a low-protein diet, thiamine deficiency, alcoholism, and hypothyroidism. As the medicinal use of cobalt has waned and measures to reduce industrial exposure have been implemented, subacute cobalt-related cardiomyopathy had become rare. However, reports describing classical features of the disease have recently surged among patients with a malfunctioning cobalt-alloy hip prosthesis. **(*Circ Heart Fail*. 2016;9:e003604. DOI: 10.1161/CIRCHEARTFAILURE.116.003604.)**

Key Words: cardiomyopathies ■ cobalt ■ heart failure ■ hip prosthesis ■ polycythemia

Approximately one-third of patients with a depressed left ventricular ejection fraction are diagnosed with nonischemic cardiomyopathy.[1] Although such patients typically have no identifiable cause for their disease, some have specific triggers, whose elimination might result in improvement in cardiac structure and function.[2] Treatable causes of cardiomyopathy include deficiencies of nutritional factors that are important for normal cardiac physiology or excessive exposure to environmental substances that can exert a depressant effect on the myocardium.[2,3] The range of potential nutritional and environmental causes for nonischemic dilated cardiomyopathy is extraordinary, but individually, they are seen rarely. As a result, when the medical history or the clinical presentation does not suggest a cause, testing for all potentially reversible etiologic factors in all patients with a nonischemic cardiomyopathy has an infinitesimally small yield and is not routinely performed in clinical practice.

Efforts to identify reversible factors would be more fruitful, if physicians were able to recognize clinical syndromes that are indicative of a specific nutritional or environmental cause. Interestingly, because they typically affect multiple organs (and not only the heart), most toxic exposures and nutritional deficiencies are associated with characteristic clinical signatures. Yet, many physicians erroneously think that the presentation of cardiomyopathy caused by a nutritional or environmental factor is indistinguishable from idiopathic forms of nonischemic cardiomyopathy.

The purpose of this review is to characterize the features of cobalt-related cardiomyopathy. Environmental contact with cobalt is commonplace because of its use in nutritional supplements, recreational or medicinal products, industrial processes, or prostheses made of cobalt alloys.[4–8] Excessive exposure to cobalt in vulnerable patients leads to a distinctive and reversible clinical syndrome.

Sources and Assessment of Human Exposure to Cobalt

Human beings can be exposed to cobalt in many ways. First, because of its use in glass, inks, and paints, occupational contact with cobalt may occur in processing plants, hard-metal industry, diamond polishing, and the manufacture of ceramics.[9–11] Second, because it can stimulate the production of red blood cells, cobalt has been used for the treatment of refractory anemia and by athletes to increase red blood cell mass and increase exercise performance, as an alternative to blood doping.[5,6] Third, cobalt is used as a component of high-performance, wear-resistant alloys that are critical in the manufacture of implanted medical devices (eg, dental

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implants, coronary artery stents, and metal orthopedic prostheses).[8,12,13] Fourth, cobalt has been used to increase foam stability in beer.[14–16] Between 1964 and 1966, 20% to 25% of all beer sold in the United States contained small amounts of cobalt.[14]

Estimation of Exposure and Biological Activity of Cobalt

Serum and urinary concentrations of cobalt are often used to estimate exposure to cobalt,[11,17] but these assays are dependent on the techniques used for the collection and analysis of the samples.[18] Increased concentrations in serum and urine is generally indicative of exposure, but are not reliably associated with adverse biological effects.

Although increased serum concentrations of cobalt has been proposed as a means of identifying patients with a hip arthroplasty who are experiencing excessive wear,[19–23] such measurements may not be useful in selecting patients who require surgical revision or who may be experiencing cobalt-related organ toxicity.[24–26] There are no US Food and Drug Administration–approved assays for the measurement of cobalt in human samples[27]; there are no data to inform which type of sample (blood, serum, urine, or tissue) should be evaluated (the United Kingdom regulatory authority recommends only testing of whole blood); there is no standardized approach to the collection of samples to prevent metal ion contamination of the samples (eg, by the use of trace metal–free tubes); there are no standardized procedures for the performance of metal ion assays by commercial laboratories; there is inadequate information about the factors that can cause interference with the test results; there are no quality assurance procedures to ensure that the results of assays are accurate and reliable; and there are no validated thresholds for the interpretation of normal or toxic values for the test results. Importantly, no specific serum or urine concentration of cobalt is reliably associated with systemic toxicity or can be used to assess the role of cobalt in any specific disease. The lack of utility of serum or urine cobalt determinations is likely related to the fact that neither measures the level of free intracellular biologically active cobalt.[7,18] Although the measurement of cobalt in red blood cells might provide a more reliable estimate of intracellular levels,[18,28] it is not known if erythrocyte cobalt concentrations can be used to assess the role of cobalt in the development of organ dysfunction.

Some studies have assessed the risk of organ-specific toxicity by measuring tissue concentrations of cobalt. Assays of cobalt have been performed in myocardial tissue,[29] but these results are highly dependent on the procedures used to prepare the tissue.[30] Moreover, the finding of an increased concentration of cobalt in myocardial tissue reflects the presence of the metal in the interstitium, but not its biological actions on cardiomyocytes, that is, an increased level of cobalt in cardiac tissue does not imply that cobalt is exerting an effect on the heart. Of note, cobalt concentrations may be elevated in cardiac tissue taken from patients with non–cobalt-related cardiomyopathies, perhaps because the cardiomyopathic process itself may promote the accumulation of cobalt within the body and the heart.[30,31]

Effect of Cobalt on the Heart in Experimental Systems

Cobalt can have both favorable and deleterious effects on the biology and physiology of the heart. Striking differences in the actions of cobalt in various studies may reflect differences between in vitro and in vivo conditions, the magnitude of cobalt exposure, and differences among species.

Role of Cobalt in Adaptation to Stress

With respect to its beneficial actions, cobalt modulates the ability of the cardiovascular system to respond and adapt to hypoxic stress. The administration of cobalt mimics hypoxic stress in several ways: (1) cobalt enhances synthesis of erythropoietin, which increases red blood cell mass and preserves tissue viability during hypoxic stress[32–35]; (2) cobalt increases the expression of hypoxia-inducible factor-1, which promotes preconditioning, reduces oxidative stress, preserves myocardial blood flow, prevents cell death and enhances myocardial differentiation and repair, and maintains myocardial function in low-oxygen conditions and other states of metabolic stress[36–41]; (3) cobalt induces vascular endothelial growth factor, which promotes angiogenesis and blood flow[42]; and (4) cobalt increases the activity of glycolysis enzymes, which allow for oxygen-independent ATP synthesis, thus preventing ATP depletion.[36,43] Exposure to cobalt also results in the formation of cobalt protoporphyrins, which exert cytoprotective and anti-inflammatory effects in the injured myocardium, thereby preventing myocardial and endothelial cell injury and adverse cardiac remodeling.[36,44–46] Moreover, cobalt normalizes blood glucose and vascular reactivity and stimulates adiponectin, thus ameliorating hypertension, diabetes mellitus, weight gain, myocardial hypertrophy, and vascular thrombosis, and in turn attenuating atherosclerotic cardiovascular risk.[47–50]

Mechanisms Underlying Cardiac Actions of Cobalt

In contrast to these beneficial actions, cobalt may interfere with the binding of calcium to the sarcolemma, the transport of calcium into the myocyte, and the inotropic effects of calcium.[51,52] In addition, cobalt can interrupt the citric acid cycle and the generation of ATP by aerobic cellular respiration,[53–55] inhibit the activity of respiratory chain enzymes and ATP production in mitochondria,[56,57] and promote the generation of reactive oxygen species.[57,58] The net result is a depression of cardiac function and changes in cardiac cell structure.[43,59–61] The characteristic findings of cobalt cardiomyopathy in experimental animals include weight loss, pericardial effusion, and low voltage on the ECG, modest histological changes with no inflammatory response on microscopy, and ultrastructural changes, including vacuolar degeneration, swollen, and distorted mitochondria with loss of cristae, features similar to those seen in the reversible experimental cardiomyopathy induced by alcohol and by thiamine or protein deficiency.[55,62–65] The only pathological finding that may be pathognomonic for cobalt-induced heart disease is the presence of dense osmophilic intramitochondrial particles.[62,66,67]

Although the potential for adverse effects of cobalt on the heart is well known, mitochondrial function and cardiac contractility generally do not change, despite significant

accumulation of cobalt in the myocardium,[40,68,69] suggesting that conditions other than exposure to cobalt play an important role in mediating or potentiating the effects of the ion. In experimental studies where cobalt alone exerted minimal adverse cardiac effects, the toxicity of cobalt became manifest in the presence of hypothyroidism or by the consumption of a low-protein, low-thiamine diet.[63,67] This potentiation may be explained by the fact that a deficiency of thiamine, a deficiency of thyroxine, and the presence of cobalt act at the same enzymatic sites to interfere with the normal functioning of the citric acid cycle,[70–74] explaining why the ultrastructural changes in the myocardium produced by cobalt are mimicked experimentally by thiamine deficiency, a low-protein diet, and hypothyroidism.[54,64,65,70,75] Of note, dietary protein may modulate the absorption of cobalt and potentiate the development of goiter,[16,76–78] and cobalt may not only suppress the synthesis of thyroxine[79–81] but may also act to antagonize its peripheral actions.[81,82] As a result of these synergistic interactions, cobalt toxicity, dietary protein and thiamine deficiencies, and hypothyroidism routinely coexist.

Effect of Cobalt on the Heart in Human Beings

Healthy people who take cobalt as a dietary supplement may consume ≤1000 μg daily, and expert governmental advisory groups have concluded that supplementation ≤1400 μg/daily (which results in whole blood levels of ≤18 μg/L) produces no adverse health effects.[4]

The effects of cobalt on the production of red blood cells and thyroxine occur more predictably and at lower levels of exposure than effects on other organs.[4,83,84] This observation explains why regulatory agencies and environmental safety organizations have developed recommendations concerning the level of safe exposure based on clinical studies that primarily evaluated changes in hemoglobin and thyroid function. Because the effects on the heart are seen only at higher concentrations, cobalt cardiotoxicity is predictably preceded and accompanied by polycythemia and hypothyroidism.

The diagnosis of cobalt cardiomyopathy requires (1) demonstration of biventricular dilatation and systolic dysfunction at a time when blood/tissue concentrations of cobalt are increased; and (2) normalization of cardiac structure and function when exposure ceases and blood/tissue concentrations of cobalt decline into range close to that expected in nonexposed individuals (in the absence of other interventions for the treatment of cardiomyopathy). Although some have suggested that cobalt may impair diastolic filling without affecting systolic function, echocardiographic evidence of diastolic dysfunction is a common finding in middle-aged to elderly people,[85,86] and thus, its presence cannot reliably distinguish people who have been exposed to cardiotoxic substances from unexposed controls.[87]

Cardiomyopathy in Patients Receiving Cobalt for the Treatment of Anemia

Cobalt salts were first introduced as a treatment for anemia in the 1930s and continued to be prescribed until the 1970s,[6,88–90] when the practice was discontinued because of the development of reversible goiter and hypothyroidism.[79,91,92] The doses of cobalt used to stimulate erythropoiesis ranged from 25 to 150 mg daily of cobalt chloride, which delivered 11 to 68 mg of cobalt daily and would be expected to yield whole blood cobalt concentrations ranging from 62 to 890 μg/L[4]; however, the measurements reported in anemic patients were performed only in serum. The ingestion of 25 to 50 mg of cobalt chloride was associated with serum concentrations of 400 to 1000 μg/L and of 80 to 890 μg/L in anephric patients[6] and hemodialysis patients,[93] respectively. Serum cobalt concentrations of 750 to 1950 μg/L were reported in patients treated with cobalt who developed reversible hypothyroidism.[79,91] Despite these extremely high levels of cobalt (often sustained for long periods of time), it was long believed that no cases of cobalt cardiomyopathy or heart failure were reported during the 40 years that cobalt salts were used for the treatment of anemia.[94]

A thorough review of the medical literature, however, reveals 2 reports of cardiomyopathy in patients receiving cobalt for the treatment of anemia.[95,96] A 1958 report[95] described a child with subacute onset of cardiomyopathy and congestive heart failure after treatment with an iron-cobalt supplement. The patient had difficulty gaining weight, polycythemia, suspected pericardial effusion, tachycardia, hepatomegaly, and a massive goiter. The physicians caring for the child made the diagnosis of cobalt-induced hypothyroidism, which they believed led to cardiomyopathy; the cardiomyopathy resolved after the withdrawal of cobalt and the treatment of hypothyroidism. Similarly, a 1984 report[96] described a child receiving cobalt for anemia, who presented with a history of weight loss, subacute onset of cardiomyopathy, and congestive heart failure, hypothyroidism, polycythemia, metabolic acidosis, and hypotension; the serum cobalt concentration was 270 μg/L. The clinical features of these 2 patients are strikingly similar to the findings in cobalt cardiomyopathy in the experimental setting[55,62,63] and the descriptions of beer-drinkers' cardiomyopathy.[14–16]

Cardiomyopathy in Nutritionally Deficient Drinkers of Cobalt-Fortified Beer

In the mid-1960s, breweries began to add cobalt to beer to restore and stabilize the foam, which is destroyed when synthetic detergents are used to clean glassware.[97] With the advent of cobalt fortification, physicians in Quebec City, Minneapolis, Omaha, and Belgium began seeing heavy beer drinkers who presented with a cardiomyopathic syndrome that was distinct from that generally seen with alcoholic cardiomyopathy.[14–16,98–101] Typically, patients were white, aged 40 to 50 years, who were heavy beer drinkers with severe long-standing malnutrition or thiamine deficiency, and often with a history of significant lethargy, anorexia, and weight loss in the months preceding the illness. Despite the absence of cardiac risk factors, the patients presented with severe biventricular heart failure, which was distinguished by its abrupt onset; the frequent presence of pericardial effusion and polycythemia; the presence of low voltage on the ECG with the absence of cardiac arrhythmias; predominant abdominal symptoms with tender hepatomegaly; rapid clinical progression leading to cyanosis, marked elevation or cardiac and hepatic enzymes, lactic acidosis, and shock; and a high mortality rate (of 10%–40%), which was proportional to the daily intake of beer.[14–16,98–101] In those who died, the histological examination of the heart

was generally unremarkable; however, electron microscopy showed characteristic vacuolar degeneration and loss of myofibrils, coiled and degenerated remnants of intercalated discs, swollen and distorted mitochondria with absent cristae with dense inclusions, and dilated sarcoplasmic reticulum.[14,102,103] Most deaths occurred within days of hospital admission, but in those who did not die, recovery was generally rapid and complete with normalization of cardiac function and exercise tolerance, even in patients who continued heavy beer consumption.[104]

The features of beer-drinkers' cardiomyopathy were readily distinguishable from those with idiopathic nonischemic dilated cardiomyopathy (Table 1). Typically, patients with beer-drinkers' cardiomyopathy had a previous history of anorexia and weight loss, the rapid onset of heart failure, the presence of pericardial effusion, polycythemia and thyroid abnormalities, and a clinical picture dominated by peripheral hypoperfusion (ie, hypotension, lactic acidosis, and cyanosis). The syndrome in beer drinkers resembled beriberi heart disease, except for the absence of a therapeutic response to treatment with thiamine.[15,100]

Although physicians in Quebec concluded that cobalt fortification played an important role in the development of beer-drinkers' cardiomyopathy, the primary support for a causal role for cobalt was chronological, that is, the disease appeared soon after the onset of cobalt fortification by brewers and the disease disappeared after the decision by brewers to discontinue the use of cobalt additives.[100] However, many aspects of the syndrome were inconsistent with an etiologic role for cobalt: a peculiar geographical distribution, the great variation in the amount of beer ingested, the absence of the disease in brewery workers, the occurrence of the disease in drinkers of beer not fortified with cobalt, and the absence of the disease in countries with higher per capita beer consumption, including beer containing cobalt.[104] Furthermore, the amount of cobalt added to beer was small; even heavy drinkers consumed <10 mg daily, which was far less than the amount of cobalt ingested when cobalt was used to treat anemic patients, who (despite high doses of cobalt) did not generally develop cardiomyopathy or acute biventricular failure.[14,105] Although myocardial levels of cobalt in a few patients with beer-drinkers' cardiomyopathy who died were high,[29] the significance of this finding is unclear. Tissue levels of cobalt persist for long periods after cessation of exposure; yet, the patients who survived the initial presentation recovered rapidly and fully (despite presumed persistence of cobalt in the myocardium).[16]

For these reasons, Alexander et al[14,98] proposed that beer-drinkers' cardiomyopathy was a multifactorial disease, which developed when short-term exposure to cobalt exerted a cardiodepressant action in hearts whose function had been significantly impaired by the direct effects of alcohol and by severe coexisting protein and thiamine deficiency. This hypothesis is consistent with observations in animal models, which showed no cardiomyopathy with cobalt exposure alone but a severe cardiomyopathy when cobalt exposure was preceded by protein deficiency[63,67,106]; in another experimental study, the effects of cobalt on the heart were exacerbated when alcohol was administered at the same time.[54] Other factors (eg, genetic factors) may also be required for the development of beer-drinkers' cardiomyopathy because the syndrome developed in only a small fraction of the exposed population.[16]

A critical reappraisal of the medical reports indicates that cobalt-induced hypothyroidism probably played a heretofore-unrecognized role in the development of beer-drinkers' cardiomyopathy. Affected patients showed histological changes in the thyroid that are similar to those seen in industrial workers exposed to cobalt[102,107]; these changes were the seminal clue that first led clinicians to suspect a role for cobalt.[108] Many clinical aspects of the beer-drinkers' syndrome are similar to those seen in hypothyroidism (ie, months of fatigue and anorexia preceding onset, dilated cardiomyopathy, large pericardial effusions, and marked elevation of cardiac and hepatic enzymes).[109–115] Furthermore, exposure to cobalt is far more likely to adversely affect the thyroid than the heart,[17] and hypothyroidism has been shown to exacerbate the cardiac effects of cobalt in experimental animals.[67] Thus, cobalt-induced hypothyroidism (and not a direct action of cobalt on

Table 1. Features Distinguishing Cobalt-Related Cardiomyopathy From Nonischemic Dilated Cardiomyopathy Unrelated to Heavy Metal Exposure

	Non–Cobalt-Related Nonischemic Dilated Cardiomyopathy	Cobalt-Related Cardiomyopathy
Predisposing factors other than cobalt	None	Low-protein diet, thiamine deficiency, hypothyroidism
Recent medical history	Variable and nonspecific	Recent history of anorexia and weight loss
Clinical presentation	Typically asymptomatic or slowly progressive left ventricular dysfunction	Rapid onset and progression of severe heart failure
Electrocardiographic changes	Nonspecific changes or poor R-wave progression	Low voltage across all ECG leads, sinus tachycardia, absence of cardiac arrhythmias
Echocardiographic changes	Enlargement and depressed systolic function of both ventricles	Pericardial effusion, enlargement and depressed systolic function of one or both ventricles
Laboratory findings	No typical findings	Polycythemia, hypothyroidism, elevated enzymes, and lactic acidosis
Clinical course	Typically slowly progressive over months to years	Rapidly progressive course with cyanosis, hypotension
Clinical outcome	Infrequently reversible, low short-term mortality rate	High short-term mortality rate, but survivors experience complete cardiac and clinical recovery

the heart) may have been responsible for the reports of beer-drinkers' cardiomyopathy in nutritionally deficient alcoholics in the mid-1960s.

Increased Myocardial Cobalt Levels in Patients With End-Stage Renal Disease

In the late 1970s, 2 patients with end-stage renal disease had increased myocardial levels of cobalt while receiving cobalt therapy for anemia.[107,109] In one case,[116] no clinical history or findings were reported. A second patient presented with rapidly progressive heart failure because of a cardiomyopathy[117]; the patient had a pericardial effusion and was likely to be treated with a low-protein diet (for the management of their advanced renal disease), and thus, had features reminiscent of the cardiomyopathy found in beer drinkers.

Identification of the role of cobalt in the development of cardiomyopathy in patients on hemodialysis is complicated by the fact that severe renal insufficiency is independently associated both with cardiomyopathy and pericardial effusion and with cobalt accumulation (even in the absence of any exogenous or endogenous cobalt source).[118] Therefore, the simultaneous finding of high cardiac cobalt levels and cardiomyopathy in patients on hemodialysis may be explained by the fact that each is associated with end-stage renal disease rather than cobalt being the cause of cardiac dysfunction.[119–121] Given their limited ability to excrete cobalt, increased blood and tissue concentrations of cobalt were common in patients with end-stage renal disease who were treated with cobalt for anemia.[6,116] The extreme rarity of well-described reports of cardiomyopathy in these patients (despite the additional risk related to the therapeutic use of a low-protein diet) suggests that cobalt is not a cause of cardiomyopathy in end-stage renal disease.

Cardiomyopathy in Industrial Workers Exposed to Cobalt

Industrial workers have been exposed to cobalt for decades, and such exposure may be associated with high concentrations of cobalt in both blood and tissues. In workers exposed to pure cobalt dust, the concentration of cobalt in whole blood has ranged from 50 to 1000 μg/L[17,122] comparable with the levels reported with the use of cobalt for the treatment of anemia.[72] The biological and clinical effects of cobalt may depend on whether the worker is exposed to pure cobalt or to cobalt mixtures that contain other metals. Specifically, concomitant exposure to tungsten increases the bioavailability and tissue reactivity to cobalt.[12,123–125]

Although workers exposed to cobalt may experience dyspnea, this symptom has been attributed to effects on pulmonary (rather than cardiac) function.[17] Toxic effects of cobalt–tungsten mixtures in the lungs may lead to cor pulmonale, with secondary effects on right ventricular function.[126,127] One study reported nonspecific changes in several echocardiographically determined left ventricular filling parameters in cobalt workers,[128] but these may have been related to the higher incidence of asthma in cobalt workers rather than a direct effect of cobalt on the heart.[128–130] Studies of cardiac function in cobalt-exposed workers have generally revealed no impairment of left ventricular systolic function,[126–128] and thus, Linna et al[128] concluded that no major cardiac dysfunction could be directly attributed to cobalt exposure in the workers that they evaluated.

Despite the large number of industrial workers, reports of cardiomyopathy have been exceptionally rare, with only 7 cases over a 20-year period[94,131,132] describing heart failure or cardiogenic shock in individuals exposed to cobalt mixtures in the hard metal industry. These cases were characterized by the subacute onset of heart failure, dilated cardiomyopathy, sinus tachycardia, low voltage on ECG, pericardial effusions, polycythemia, cyanosis, hypotension, and goiter.[94,132] Thus, the clinical features were similar to that reported in beer-drinkers' cardiomyopathy.

Despite unequivocal exposure to environmental cobalt, exposure to the metal ion may not have been the only cause of cardiomyopathy reported in industrial workers. Three of the cases reported by Vermel' et al[132] had concomitant alcoholism; alcohol can potentiate the cardiac effects of cobalt,[54] and alcohol abuse can be accompanied by acute heart failure, cardiomyopathy, and polycythemia in the absence of cobalt.[133] Furthermore, hard metal workers are exposed not only to cobalt but to other metals and minerals, which may have their own adverse effects on the heart or may be a required cofactor in the toxicity of cobalt.[9,10,123–125,134,135] Exposure to noncobalt industrial metals may explain the report of cardiomyopathy in 2 workers in a mineral assay laboratory.[136] Neither patient had any of the clinical features (polycythemia, pericardial effusion, or hypothyroidism) that are characteristically seen in patients with cobalt-related cardiomyopathy; tissue levels of cobalt were far lower than those reported in typical cases of cobalt-related heart disease; and ultrastructural changes in the heart differed from those seen in cobalt-related cardiomyopathy.[14,102,103,136] Christensen and Poulsen[137] noted thyroid abnormalities but not cardiomyopathy in their evaluation of pottery painters, who are exposed to only cobalt but not to other potentially toxic compounds. Thus, the totality of epidemiological evidence is not sufficient to prove a role for cobalt in inducing cardiomyopathy in cobalt-exposed industrial workers.[138,139]

Cardiomyopathy in Patients With Total Metal Hip Replacement or Arthroplasty

Cobalt alloys have been used in hip arthroplastic procedures since 1938, and increased concentrations of cobalt in blood, hair, and urine have been reported in patients receiving cobalt alloy implants since 1967.[140,141] In patients who undergo metal-on-metal hip arthroplasty, corrosion, and wear produce metal debris in the form of nanoparticles, which can enter the bloodstream and be deposited in distant tissues with the subsequent release of cobalt ions.[142,143] Serum levels of cobalt increase after implantation of these prostheses[144–146] and decline after explantation.[147,148] Despite the extra-articular exit of cobalt, serum or blood levels of cobalt are low (<10 μg/L) in the majority of implant patients[19] but may be increased to higher levels in patients with excessive wear, particularly those requiring surgical revision.[149–151] Although concerns have been raised about the long-term biological effects of higher-than-normal serum levels of cobalt, such increased concentrations do not cause systemic toxicity in most patients.[27] The paucity of reports of toxicity in patients with a cobalt alloy prosthesis may be related to the ability

of the kidney to dramatically enhance the renal clearance of cobalt in patients whose cobalt load is increased by the presence of a prosthesis.[152]

No reports of cardiac disorders were linked to the presence of cobalt implants until 2009, although exposures to prosthetic sources of cobalt have been sustained in patients for as long as 30 years.[140] A small case–control study suggested that patients with a metal-on-metal hip resurfacing had slightly larger left ventricles with slightly lower ejection fractions, but the 2 groups exhibited few abnormal values and were not matched for cardiovascular confounders.[153] A comprehensive review of the medical literature reveals 15 patients (described in 17 reports[154–170]) who had a cardiac disorder that was attributed to a cobalt alloy prosthesis (Table 2). Of these, 8 patients[162–170] had a documented nonischemic (often nondilated) cardiomyopathy with dramatically increased serum or blood levels of cobalt (>300 μg/L), which were associated with hypothyroidism, polycythemia, weight loss, and pericardial effusion. Lower levels of cobalt were not associated with meaningful cardiac toxicity.[83,84]

Summary and Conclusions

Exposure to cobalt, related to medicinal or recreational ingestion or industrial contact, can cause a reversible depression of cardiac systolic dysfunction, which can be readily distinguished from other forms of nonischemic dilated cardiomyopathy. Patients presenting with rapid onset of cardiomyopathy, who also have polycythemia, pericardial effusion, or goiter should be evaluated for cobalt exposure. Such exposure can be confirmed by the measurement of the concentration of cobalt in serum or whole blood, but such levels are not necessarily predictive of or correlate with clinical cardiotoxicity. The clinical emergence of cobalt cardiomyopathy requires the coexistence of one or more cofactors, particularly a low-protein diet, thiamine deficiency, alcoholism, and hypothyroidism. As the medicinal use of cobalt has waned and measures to reduce industrial exposure are implemented, cobalt-related cardiomyopathy had become rare, but now, some patients with a malfunctioning metal hip prosthesis and markedly increased serum or blood cobalt levels are exhibiting characteristic features of the disease.

Table 2. Clinical Features of Heart Disease Reported in Patients With a Cobalt Alloy Prosthesis

Study	Age/Sex/Medical History	Serum Cobalt	Cardiac Abnormalities Reported	Clinical Outcome
Poorly documented cases with unlikely relation to cobalt				
Tower[154–156]	49 M	83 μg/L	Diastolic dysfunction without specific abnormalities, no systolic dysfunction	Poorly documented
Tower[154–156]		23 μg/L		
Sotos and Tower[157]		122 μg/L		
Pelclova et al[158]	56 M, multiple CV risk factors; hypothyroidism	139 μg/L	Pericardial effusion, hypertension, LV hypertrophy, no cardiomyopathy	Not reported
Apel et al[159]	65 M, hypothyroidism	…	Poorly documented pericardiomyopathy	Not reported
Machado et al[160]	75 M, multiple CV risk factors	13.5 μg/L (230 nmol/L)	Coronary artery disease, systolic dysfunction with symptoms of heart failure (EF 21%)	EF 45% after β-blockade and surgical revision (serum cobalt 4.5 μg/L [77 nmol/L])
Samar et al[161]	54 M	120 μg/L	LV/RV dysfunction; MRI hyperenhancement	Continued clinical deterioration despite prosthesis removal
Better documented cases with plausible relation to cobalt				
Oldenburg et al[162]	55 M, hypothyroidism, weight loss	625 μg/L	Moderate systolic dysfunction, sinus tachycardia	Not reported
Gilbert et al[163] and Zywiel et al[164]	46/52 M, hypothyroidism, polycythemia, weight loss	6521 μg/L (whole blood)	Rapidly progressive heart failure, hypotension, EF 10%, pericardial effusion	Death despite chelation therapy
Allen et al[165]	59 F, hypothyroidism	287.6–398.6 μg/L	EF 25%, LV (but no RV) hypokinesis but no dilatation, pericardial effusion	Recovery after heart transplantation and removal of prostheses
Giampreti et al[166]	75 M	352.6 μg/L	EF 32%, LV (but no RV) global hypokinesis, pericardial effusion	EF 55% after chelation therapy
Dahms et al[167]	55 M, hypothyroidism	15 000 nmol/L	EF 25%, global hypokinesis	EF 40% after chelation therapy
Mosier et al[168]	54 M	189 ppb	LV/RV dysfunction, MRI hyperenhancement	Progression despite prosthesis removal and fall to 16 ppb
Khan et al[169]	69 F, pericardial effusion	200–300 ng/mL	LV/RV dysfunction without dilatation, MRI enhancement, pericardial effusion	Ventricular assist device implantation, death
Fox[170]	60 F, weight loss	424–642 μg/L whole blood	EF 35% to 40%, global LV hypokinesis	Cardiogenic shock, death

CV indicates cardiovascular; EF, ejection fraction; LV, left ventricle; MRI, magnetic resonance imaging; and RV, right ventricle.

Disclosures

Dr Packer has consulted for Admittance, Amgen, AstraZeneca, Bayer, BioControl, Boehringer Ingelheim, Cardio3, Cardiokinetix, Cardiorentis, Cytokinetics, Daiichi Sankyo, GlaxoSmithKline, Novartis, Takeda, and ZS Pharma.

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