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Brian Darrith

Tahsin M. Rahman

Karthikeyan Ananthasubramaniam

Chris Culvern

Joshua J. Jacobs

See next page for additional authors

Authors

Brian Darrith, Tahsin M. Rahman, Karthikeyan Ananthasubramaniam, Chris Culvern, Joshua J. Jacobs, and Craig Silverton

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Brian Darrith, MD [a], Tahsin M. Rahman, MD [a, b], Karthikeyan Ananthasubramaniam, MD, FACC [c], Chris Culvern, MS [d], Joshua J. Jacobs, MD [d], Craig D. Silverton, DO [a, *]

[a] Department of Orthopaedic Surgery, Henry Ford Hospital, Detroit, MI
[b] Wayne State University School of Medicine, Detroit, MI
[c] Department of Cardiology, Henry Ford Hospital, Detroit, MI
[d] Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL

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ABSTRACT

Background: The purpose of this study is to determine if there is a difference in echocardiographic results between patients with metal-on-metal (MoM) vs non-MoM total hip arthroplasty (THA) and to determine if a correlation exists between serum metal levels and echocardiographic outcomes.
Methods: Seventy-five patients with the same modular THA enrolled in this prospective cohort study, and 49 had MoM bearings. All patients had serum cobalt, chromium, and titanium levels drawn at 2 study visits with a transthoracic echocardiogram at the second visit. Serum metal concentrations and echocardiographic parameters were compared with 2-way t-tests. Multiple linear regression analyses identified any significant predictors of echocardiographic outcomes.
Results: Mean serum cobalt and chromium levels were significantly greater in the MoM group at both time-points ($P < .001$ and $P < .05$, respectively). Titanium levels were similar between groups ($P > .05$). MoM patients had significantly lower global longitudinal strain compared with the non-MoM group (18.4% vs 20.2%; $P = .026$). Serum cobalt concentration was found to be an independent predictor of tricuspid annular plane systolic excursion ($P = .02$).
Conclusion: MoM THA bearings are associated with increased serum cobalt and chromium levels. Patients with MoM THAs had decreased global longitudinal strain, a measure of left ventricular function, but both groups remained within normal range. The clinical impact of the positive association between serum cobalt concentration and tricuspid annular plane systolic excursion, a marker of right ventricular function, deserves further study. These findings can reassure physicians and patients that metal-induced cardiomyopathy is not typical in the setting of MoM THA.
Level of Evidence: Level II, Prospective Cohort Study.

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Initially designed as an alternative to metal-on-polyethylene implants, metal-on-metal (MoM) total hip arthroplasties (THAs) have been increasingly scrutinized for complications including both local and systemic metal toxicity and higher than expected revision rates [1–10]. The Food and Drug Administration has recalled several MoM THA components no longer available in the United States. However, there continue to be many patients with MoM THAs in situ that require monitoring for adverse effects related to local and systemic dissemination of metal debris.

Several studies have shown that wear of MoM bearings can lead to the release of implant-derived cobalt and chromium both locally in the joint and also systemically via the vascular and lymphatic

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* Reprint requests: Craig D Silverton, DO, Department of Orthopaedic Surgery Henry Ford Hospital, 2799 West Grand Boulevard, CFP-6 Detroit, MI 48202.

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systems [2–10]. Previous studies have reported adverse local tissue reactions associated with MoM arthroplasty, including periprosthetic tissue necrosis and pseudotumor formation [11–16]. Systemic cobalt toxicity associated with hip arthroplasty is relatively rare compared with local toxicity. Potential for cobalt-induced cardiotoxicity has been known since the 1960s when it was reported to cause cardiac dysfunction in Quebec beer drinkers [17,18]. Pathophysiologic changes of cardiac function have been attributed to cobalt's high affinity for sulfhydryl groups resulting in impaired Krebs cycle oxidation and chronic inhibition of sympathetic tone [17–20]. Large population echocardiographic studies in factory workers routinely exposed to cobalt have shown early left ventricle (LV) diastolic dysfunction without overt clinical disease [17–20]. Owing to the small number of reported cases of systemic disease secondary to metal release from THA implants, research has been limited to case reports of severe clinical manifestations [21–25]. Little is known regarding the prevalence of mild, subclinical cardiac effects. Furthermore, a dose-dependent relationship between elevated serum metal levels and the development of systemic adverse reactions is not well established [26,27]. A cross-sectional study compared patients with non-MoM THA to patients with MoM hip resurfacing and reported a decreased mean ejection fraction (EF) in the MoM cohort [28]. Another study performed cardiac MRI and cobalt and chromium levels on patients with MoM or ceramic-on-ceramic bearings and found no relationship between cardiac function and bearing type or cobalt and chromium levels [29]. Further investigation is warranted to determine the risk of cardiac dysfunction in patients with MoM hip arthroplasty.

The purpose of our study is (1) to determine if a significant difference exists in echocardiographic measures between patients with MoM and non-MoM THAs and (2) to determine if a correlation exists between serum cobalt and chromium levels and the development of echocardiographic changes.

Methods

The same senior surgeon implanted a single design dual-modular femoral component (Profemur Z; Wright Medical Group Inc., Memphis, TN), with the same titanium modular neck and stem, in 152 patients between 2004 and 2010 at a single teaching hospital. Patients were identified by chart review of the single surgeon's case log. After receiving institutional review board approval, 137 of the 152 consecutive patients were contacted for enrollment in this study. The remaining 15 patients were unable to be contacted despite multiple attempts. Of the 137 approached for enrollment, 75 patients consented for participation in this prospective cohort study. Inclusion criteria included history of Profemur Z implantation during primary THA by the single surgeon. All of the femoral components were dual-modular, with titanium stems and titanium necks. Of the 75 patients enrolled, 49 patients had a MoM articulation while 26 patients had a non-MoM THA articulation. Seventeen of the 49 MoM THAs utilized a monoblock cobalt-chromium cup, and the remaining acetabular components were composed of a titanium shell and a modular liner which, depending on the femoral head material, was polyethylene, ceramic, or cobalt-chromium. THAs with MoM articulations consisted of a cobalt-chromium femoral head and acetabular liner while non-MoM joints included either ceramic or cobalt-chromium heads and polyethylene or ceramic liners. Exclusion criteria included any diagnosis of heart disease before THA.

Patients were assessed at 2 time points. The first time point (subsequently referred to as "early") was at least 2 years post-THA. At this time, serum cobalt, chromium, and titanium concentrations were obtained. The second time point (subsequently referred to as "late") was a minimum 6 years post-THA, and at this time metal concentrations were repeated, and echocardiograms were performed. The Charlson Comorbidity Index was calculated for all patients at this visit [30]. Patients with abnormal echocardiograms were subsequently seen within the institution's cardiology department, and the diagnosis of heart failure or cardiomyopathy was tracked for each patient.

All serum metal concentrations were analyzed by the Mayo Clinic Laboratory using inductively coupled plasma-mass spectrometry on venous blood samples (Rochester, MN). Detection limits were 1.0 ng/mL for titanium, 0.1 ng/mL for cobalt, and 0.1 ng/mL for chromium. Transthoracic echocardiography was done using a GE Logiq ultrasound machine (General Electric, Buckinghamshire, UK) by a trained sonographer. The same sonographer performed all echocardiograms following the American Society of Echocardiography guidelines. A National Board of Echocardiography certified cardiologist, blinded to the type of THA bearing, read the echocardiograms measuring left ventricular EF, global longitudinal strain (GLS) [31], pulmonary arterial pressure, and tricuspid annular plane systolic excursion (TAPSE) [32].

The following American Society of Echocardiography criteria and techniques were used for echocardiographic measurements [33–35]. Apical 4 and 2 chamber views were used to assess left ventricular ejection via the Biplane Simpson method with 3 consecutive beats in sinus rhythm and GLS, using speckle tracking analysis via the GE Echopac software (General Electric). GLS is a quantifiable measure of left ventricular function based on longitudinal shortening. Pulmonary artery systolic pressure was measured by identifying the highest peak tricuspid regurgitation velocity and calculating the difference in between right ventricular and atrial pressure using the modified Bernoulli equation. Inferior vena cava collapsibility was done to derive right ventricular systolic pressure and hence pulmonary artery pressure. Longitudinal excursion of lateral tricuspid annulus (TAPSE) was assessed by placing M-mode cursor on the lateral tricuspid annulus to assess the excursion of the annulus in systole. TAPSE is a measure of right ventricular function based on the mechanical response of the tricuspid valve during right ventricular contraction.

Statistical Methods

Statistical analyses were performed using Stata 14.2 (StataCorp, College Station, TX). Student's t-tests and Fischer Exact tests were conducted to compare continuous and categorical variables between MoM and non-MoM groups. For variable distribution departed from normality, Wilcoxon Rank-Sum tests were used. Echocardiographic outcomes were compared between patients with and without elevated serum metal levels, with >7 ng/mL used as the cutoff. Pearson correlation tests and multiple linear regressions were conducted to identify any significant predictors of echocardiographic outcomes while accounting for all available covariates, including gender, age, BMI, cup size, head size, time elapsed until echocardiogram, diagnosis of hypertension or thyroid disease, history of bilateral THA, and Charlson comorbidity index.

Post-hoc power analysis was performed (G*Power 3.1.9.4, 2009) which showed a power greater than 0.8 for the following analyses: TAPSE linear regression and t-tests comparing metal concentrations and echocardiographic parameters between groups.

Results

Patient demographics were similar between cohorts with the exception of height and head size (Table 1). Additionally, when stratifying the non-MoM cohort by ceramic vs metal heads, patients with ceramic heads were younger at the time of surgery than patients with metal-on-polyethylene bearings ($P = .001$; Appendix

Table 1
Patient Demographics.

Variables	Total (n = 75)	MoM Cohort (n = 49)	Non-MoM Cohort (n = 26)	*P* Value
Age (y)	57.96 ± 11.45	57.59 ± 9.8	58.65 ± 14.24	0.705[a]
BMI	33.63 ± 6.29	33.58 ± 6.35	33.72 ± 6.30	0.863[a]
Height (cm)	155.65 ± 30.65	149.35 ± 35.51	167.73 ± 10.93	0.014[a]
Weight (Kg)	110.34 ± 38.11	114.17 ± 0.60	102.5 ± 31.81	0.249[a]
CCI	1.89 ± 1.58	1.92 ± 1.55	1.85 ± 1.62	0.893[a]
Gender				1.000[b]
Male	36 (48%)	24 (49%)	13 (50.0%)	
Female	39 (52%)	25 (51%)	13 (50.0%)	
Side				0.473[b]
Left	33 (44%)	20 (40.8%)	13 (50%)	
Right	42 (56%)	29 (59.2%)	13 (50%)	
Neck Length				0.397[b]
Short	57 (76%)	39 (79.6%)	18 (69.2%)	
Long	18 (24%)	10 (20.4%)	8 (30.8%)	
Bilaterial THA	24 (34.8%)	16 (34%)	9 (39.1%)	0.7922
Stem size (mm)	4.05 ± 1.54	3.94 ± 1.55	4.27 ± 1.54	0.380[a]
Cup size (mm)	54.19 ± 4.30	53.71 ± 4.53	55.08 ± 3.76	0.194[a]
Liner size (mm)	40.12 ± 6.93	41.4 ± 7.28	38.36 ± 6.16	0.120[a]
Head length (mm)	1.53 ± .77	1.6 ± .77	1.42 ± .76	0.360[a]
Head size (mm)	39.38 ± 5.78	40.86 ± 5.89	36.48 ± 4.37	0.002[a]
Neck angle (degrees)				0.705[b]
0	29 (38.7%)	19 (38.8%)	10 (38.5%)	
4	1 (1.3%)	0 (0%)	1 (3.9%)	
8	33 (44.0%)	22 (44.9%)	11 (42.3%)	
15	12 (16.0%)	8 (16.3%)	4 (15.4%)	
Cup manufacture				0.210[b]
Lineage	9 (12.5%)	4 (8.2%)	5 (21.7%)	
Conserve	18 (25.0%)	14 (28.6%)	4 (17.4%)	
Dynasty	45 (62.5%)	31 (63.3%)	14 (60.9%)	
Thyroid disease prior to echo	6 (8%)	5 (10.2%)	1 (3.8%)	0.658[b]
Diabetes mellitus	13 (17.3%)	9 (18.4%)	4 (15.4%)	1.000[b]
Hypertension prior to echo	53 (70.7%)	34 (69.4%)	19 (73.1%)	0.796[b]
Chronic kidney disease	4 (5.3%)	2 (4.1%)	2 (7.7%)	0.606[b]
Aspirin use	30 (40%)	19 (38.8%)	11 (42.3%)	0.808[b]

MoM, metal-on-metal, BMI, body mass index, CCI, Charlson Comorbidity Index.
[a] Student t-test, alpha = 0.05 as significant.
[b] Fisher Exact test, alpha = 0.05 as significant.

1). Cobalt and chromium concentrations were significantly higher in MoM patients at both time points, but serum titanium concentrations and cobalt-chromium ratios were not significantly different between MoM and non-MoM groups (Table 2). Cobalt and chromium levels were also similar between non-MoM cohorts stratified by ceramic vs metal heads (Appendix 2). There was a significant increase in serum cobalt ($P = .015$) and chromium ($P = .036$) levels between time-points in the MoM group but not the non-MoM group, and there was no significant difference in serum titanium or cobalt-chromium ratio ($P > .05$) in either group (see Table 2 for mean values at each time-point). The only difference in echocardiographic measures between groups was that MoM patients had a lower mean GLS ($P = .026$), 18.4% vs 20.2% in non-MoM patients (Table 3). There was no difference in echocardiographic outcomes when comparing the non-MoM group stratified by metal vs ceramic heads (Appendix 3).

Pearson correlation identified initial cobalt level as a significant predictor of TAPSE (r = 0.320, $P = .009$), and no other associations with echocardiographic outcomes were found to be significant in the correlation analysis. The significance of the association between cobalt levels and TAPSE was confirmed with linear regression analysis ($P = .02$; Fig. 1), and this regression model also identified weight as a significant covariate ($P = .004$).

There were no differences between cohorts of patients with and without elevated chromium or titanium levels, but patients with a cobalt concentration >7 ng/mL (n = 9) had a significantly higher mean TAPSE (2.6 cm vs 2.2 cm, $P = .04$) despite being similar to those patients without an elevated cobalt level in terms of baseline

Table 2
Comparison of Serum Titanium, Cobalt, and Chromium Concentrations and Cobalt-Chromium Ratios Between Metal-on-Metal and Nonmetal-on-Metal Cohorts.

Variables	Total (n = 75)	MoM Cohort (n = 49)	Non-MoM Cohort (n = 26)	*P* Value
Ti early (ngml)	4.43 ± 5.97	3.63 ± 2.93	5.92 ± 9.43	0.221[b]
Co early (ngml)	3.04 ± 4.56	4.36 ± 5.16	0.53 ± 0.72	<0.001[b]
Cr early (ngml)	2.31 ± 3.84	3.34 ± 4.42	0.35 ± 0.50	<0.001[b]
Co:Cr ratio early	1.7 ± 1.32	1.61 ± 1.28	1.91 ± 1.44	0.368[a]
Ti (ngml)	3.73 ± 4.68	4.16 ± 5.52	3.00 ± 2.59	1.000[b]
Co (ngml)	7.23 ± 25.52	11.12 ± 31.52	0.48 ± 0.60	<0.001[b]
Cr (ngml)	3.33 ± 8.05	5.0 ± 9.76	0.45 ± 0.67	<0.001[b]
Co:Cr ratio	1.89 ± 1.58	2.07 ± 1.84	1.53 ± 0.78	0.204[a]

MoM, metal-on-metal; Ti, titanium; Co, cobalt; Cr, chromium.
[a] Student t-test, alpha = 0.05 as significant.
[b] Wilcoxon Rank-Sum Test, used when the Student t-test cannot be used because of departures from normality, alpha = 0.05 as significant.

Table 3
Comparison of Echocardiographic Cardiac Parameters Between Metal-on-Metal and Nonmetal-on-Metal Patient Groups.

Variables	Total (n = 75)	MoM Cohort (n = 49)	Non-MoM Cohort (n = 26)	*P* Value
LV Ejection Fraction (%)	63.7 ± 7.11	63.71 ± 6.78	63.69 ± 7.83	0.943[a]
LV strain	19.08 ± 2.64	18.36 ± 2	20.21 ± 3.15	0.026[a]
Pulmonary Artery Pressure (mmhg)	26.34 ± 7.53	26.47 ± 8.36	26.09 ± 5.61	0.821[a]
Tricuspid Annular Plane Systolic Excursion (cm)	2.26 ± 0.44	2.29 ± 0.41	2.17 ± 0.49	0.419[a]
RVS'	0.13 ± 0.03	0.13 ± 0.03	0.13 ± 0.02	0.515[a]
RVe'	0.11 ± 0.03	0.11 ± 0.03	0.12 ± 0.05	0.640[a]
RVtei index (cw)	0.37 ± 0.14	0.36 ± 0.13	0.46 ± 0.18	0.141[a]
RVtei index (td)	0.44 ± 0.11	0.43 ± 0.11	0.53 ± 0.13	0.094[a]
LVtei index	0.41 ± 0.14	0.42 ± 0.14	0.33 ± 0.09	0.238[a]
Time until ECHO (y)	8.31 ± 2.47	7.38 ± 1.93	10.09 ± 2.45	<0.005[a]
SBP at Echo	133.67 ± 15.57	132.6 ± 16.59	135.6 ± 13.66	0.491[a]
DBP at Echo	75 ± 10.26	75.16 ± 10.11	74.72 ± 10.74	0.820[a]
LV size				1.000[b]
Normal	71 (94.7%)	46 (93.9%)	25 (96.2%)	
Mildly Increased	4 (5.3%)	3 (6.1%)	1 (3.8%)	
LV wall thickness				0.604[b]
Normal	45 (62.5%)	30 (62.5%)	15 (62.5%)	
Mildly Increased	27 (37.5%)	18 (37.5%)	9 (37.5%)	
LV diastolic filling (grade)				0.058
0	25 (36.2%)	13 (28.3%)	12 (52.2%)	
1	34 (49.3%)	27 (58.7%)	7 (30.4%)	
2	9 (13.0%)	6 (13.0%)	3 (13.0%)	
3	1 (1.5%)	0 (0%)	1 (4.4%)	

MoM, metal-on-metal; LV, left ventricle; RV, right ventricle; RVS', RV systolic excursion velocity; RVe', RV early diastolic tissue velocity; SBP at Echo, systolic blood pressure at the time of echocardiogram; DBP at Echo, diastolic blood pressure at the time of echocardiogram; cw, color wave; td, tissue doppler.
[a] Student t-test, alpha = 0.05 as significant.
[b] Fisher Exact Test, alpha = 0.05 as significant.

demographics (Appendix 4-6). TAPSE was the only echocardiographic parameter which differed between cohorts of patients with and without an elevated cobalt level. All 9 of these patients with a cobalt level >7 ng/mL had MoM bearings.

One patient in each cohort was diagnosed with congestive heart failure after the index echocardiogram was performed. The patient with a MoM THA was noted to have decreased LV function at the time of Echo, with a GLS of 14.2% and an EF of 50%, and the patient in the non-MoM group had diastolic dysfunction with an EF of 75% and an increased pulmonary artery pressure of 32 mm Hg. Neither of these patients had elevated metal levels.

Discussion

The purpose of our study was to determine if a significant difference exists in echocardiographic results between patients with MoM and non-MoM THAs and to characterize any significant relationships between these echocardiographic measures and serum cobalt or chromium levels. The current results demonstrate that MoM patients have a statistically significant difference in GLS compared with non-MoM patients. Additionally, when accounting for patient demographics, there is a small but statistically significant association between cobalt levels and increased TAPSE, a surrogate marker of right ventricular function.

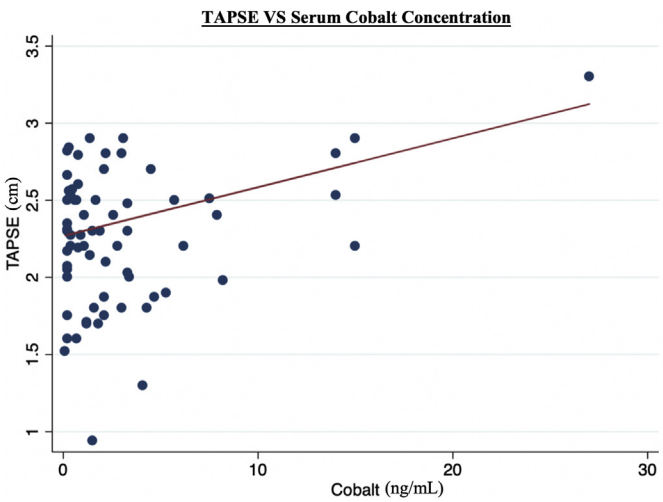

Fig. 1. Linear regression model of serum cobalt concentration vs tricuspid annular plane systolic excursion (TAPSE) (P = .002). Fit Line: TAPSE = 0.032*Cobalt +2.24 (mean weight is assumed for graphical representation).

Our study confirms prior work demonstrating the associations between MoM implants and increased serum metal levels, namely cobalt and chromium [21,23], but there was not a significant difference in cobalt-chromium ratio between groups as the average ratio in both cohorts was between 1.5 and 2.1 at all timepoints. It is important to remember that the mean ratios, reported here, are mathematically different from the ratio of the means. There was also no difference in mean titanium concentration between groups, which is reasonable given that all patients had the same titanium dual-modular femoral stem and neck. However, there was a significant increase in serum concentration of cobalt and chromium in the MoM group, suggesting a systemic accumulation of these metals over time in MoM THA patients. Identifying the source of the increased metal levels is dependent on the associated component combinations. Because all patients in the study had the same titanium, dual-modular femoral stem, it is reasonable that titanium levels were similar between groups. The source of the elevated cobalt and chromium ions in the MoM group must be the femoral head or acetabular bearing because these are the only components composed of cobalt-chromium. However, the wear could occur at the intended bearing interface between the head and acetabular liner, at the head-neck junction, or at the backside of a modular cobalt-chromium acetabular liner where it contacts the cup [3,8,13,26]. A full discussion of this topic is outside of the scope of this article, but the potential locations for corrosion and the role of implant and patient-specific factors in component wear has been discussed elsewhere [3,23,26].

The pathogenesis of cobalt-induced cardiotoxicity is the subject of much discussion. Cobalt likely interferes with energy production and myocardial contractility [36]. Both occupational and

arthroplasty-associated cobalt cardiomyopathy have been reported [37]. A review of 22 case reports of arthroplasty-associated systemic cobalt toxicity illustrates various cardiac outcomes associated with MoM THA (n = 17), MoM hip resurfacing (n = 2), and non-MoM THA (n = 3) [21,38–56]. These reports focus on cobalt toxicity, with serum concentrations ranging from 64-6022 ng/mL and 21 of 22 case patients having a cobalt level greater than 100 ng/mL. The most frequently discussed metric for cardiomyopathy in these reports was EF, with all cases having an EF less than 40% [21,22,38–56]. Ultimately, 18 of the 22 patients in these reports required revision arthroplasty, with 1of the remaining 4 patients passing away before revision, and 3 being treated conservatively with chelation therapy. Five cases resulted in patient death, with 4 passing away even after joint revision, secondary to continued cardiac dysfunction and postoperative medical complications [21,22,38–56]. In contrast to these cases of decreased EF and overt cardiomyopathy in the setting of arthroplasty-associated cobalt toxicity, the current study does not show an association between EF and serum cobalt or chromium levels. This may be because of our study not having any outlier cases of severe cobalt toxicity as was the situation in these case reports. However, there is a statistically significant difference between groups in GLS, a marker of LV contractility which is shown to be a sensitive predictor of future cardiomyopathy at GLS $\leq$16% [31]. MoM patients had a mean GLS of 18.4% as opposed to 20.2% in non-MoM patients, but both patient groups remained within normal range (>16%) [31]. Because echocardiograms were performed at 1 timepoint, we are unable to trend the GLS and other LV measurements to determine LV function over time. Therefore, despite the statistically significant difference in mean GLS between groups, we are unable to infer any clinically significant conclusions.

The current results show a significant correlation between early cobalt concentrations and TAPSE, a measure of right ventricular systolic function. In the general adult population the average TAPSE is 2.4-2.6 cm, and a TAPSE lower than 1.8 cm is considered pathologic and indicates a poor prognosis in the setting of acute cardiopulmonary dysfunction [32,57–59]. However, even if above the 1.8 cm threshold, decreases in TAPSE as little as 0.1 cm have been associated with increased risk of cardiovascular death suggesting that TAPSE is most useful as a continuous instead of a dichotomous prognostic variable [60,61]. In the current study, serum cobalt levels were predictive of increased TAPSE in both the bivariate and multivariate regression analyses. Moreover, patients with cobalt levels >7 ng/mL had a higher mean TAPSE compared with patients without elevated cobalt levels. Given that increased TAPSE is a positive prognostic factor for right ventricular function [58–61], this finding is reasonable when considered in light of the historical use of cobalt as a treatment for anemia and its more recent use as a drug to enhance cardiovascular performance [37]. By increasing the expression of hypoxia-inducible-factor-1 and vascular endothelial growth factor, cobalt enhances cardiac blood flow, myocyte differentiation and repair, and angiogenesis [37]. These beneficial effects of cobalt occur at levels much lower than those associated with systemic toxicity, but it is important to note that there is no established cutoff for the level, whether whole blood or serum, at which cobalt may become toxic [26,37]. Instead, a number of patient-specific factors modulate the risk for systemic toxicity, including nutrition status, renal failure, and thyroid disease [26,37], which we controlled for in the current study via the multiple regression analysis. The finding that modestly elevated cobalt levels in the setting of MoM THA is associated with improved cardiac function provide patient-level data to support Sabah et al in their report of cardiac failure after THA [62]. Using the United Kingdom's National Joint Registry, they matched 53,000 MoM patients with the same number of non-MoM patients and found decreased risks of cardiac failure and all-cause mortality in the MoM cohort [62]. However, this large database study lacks any patient-level laboratory or echocardiographic data to explain the reason for or significance of this association. The current study's inclusion of measures of right-heart function also expands on a prior study of left-heart function in patients with THA-associated elevations of cobalt and chromium levels which did not find any significant associations between metal levels and LV function [29]. Given the paucity of studies of right ventricular function, further studies are needed to clarify the concentration thresholds at which right ventricular function may be affected and the patient-specific comorbidities which influence the cardiac effects of systemic cobalt exposure.

There are important limitations to our study. Only 75 of the 137 contacted patients consented to the study and subsequently made it to final follow-up, which may introduce some response bias. It is a non-randomized, prospective cohort study; therefore, differences between cohorts in terms of baseline demographics may exist despite our regression analysis attempting to statistically control for such variables. Specifically, the mean duration of time-elapsed from the index THA until the echocardiogram neared statistical significance when comparing the 2 groups. This was because of the senior author's preference in using ceramic-ceramic bearings for younger patients early in the period of index surgeries, until reports of squeaking became more frequent in the literature [63], and similar complaints surfaced in clinic among ceramic-on-ceramic THA patients. Metal-on-metal THAs were used throughout the study-time period, and metal-on-polyethylene bearings were used preferentially for older patients in the latter part of the time period. After the initial period of ceramic-on-ceramic bearings, patients with metal allergies received ceramic-on-polyethylene bearings. This heterogeneity in bearing type provides another limitation to the study, although the non-MoM group was stratified by bearing type and no differences in metal ion levels or echocardiographic outcomes were shown. The change in the senior author's preference in bearing type throughout the study period accounts for the difference in time-elapsed from surgery to echocardiogram between metal-on-polyethylene vs ceramic-head combinations. However, time-elapsed since the index THA, although associated with increased serum cobalt and chromium concentrations, was not associated with any echocardiographic outcome measures. Another limitation is the inclusion of those patients with bilateral THAs within the analysis. While there was no difference in the prevalence of bilateral THAs between MoM and non-MoM groups, we did not document or account for the component composition or bearing surface of the contralateral arthroplasty. However, in an attempt to control for any possible confounding, we did consider the presence of a contralateral THA in the multivariable model, and it was not found to be significant. A further limitation is the use of echocardiography at only one time-point. Having repeat echocardiograms would allow for the trending of cardiac function in the context of patient-specific changes in metal levels. The addition of a second echocardiogram was discussed, yet it proved to be cost-prohibitive for the study's internal funding. Finally, the power of the study is limited by the number of patients who were willing to consent, and the sample size of the non-MoM cohort is particularly limited. Importantly, however, the post-hoc power analysis demonstrated that the current data are appropriately powered to determine an association between cobalt concentration and TAPSE, the only echocardiographic outcome significantly associated with any metal level throughout the analyses.

In conclusion, in the absence of overt symptoms of cardiac dysfunction, it cannot be concluded that increased metal levels secondary to THA are associated with clinically significant cardiac changes. Findings from our cohort in the context of prior studies [29,62] can serve to reassure physicians that metal-induced

cardiomyopathy is a rare, albeit possible, complication of MoM THA. There is a need for further study with the use of repeat cardiac measures over time to better understand the potential for cardiac pathology in patients with elevated cobalt levels from degradation of cobalt-alloy joint replacement components.

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Appendix

Appendix Table 1
Patient Demographics Compared Between Three Bearing Surfaces Combinations.

Variables	Total (n = 75)	MoM (n = 49)	Ceramic (n = 15)	MoP (n = 11)	*P*-Value
Age (y)	57.96 ± 11.45	57.59 ± 9.8	51.27 ± 11.71	68.73 ± 11.02	<.001[a]
BMI	33.63 ± 6.29	33.58 ± 6.35	35.17 ± 6.63	31.98 ± 5.73	.514[a]
Height (cm)	155.65 ± 30.65	149.35 ± 35.51	168.91 ± 10.76	166.35 ± 11.49	.064[a]
Weight (Kg)	110.34 ± 38.11	114.17 ± 0.60	99.71 ± 23.34	105.79 ± 40.64	.441[a]
CCI	1.89 ± 1.58	1.92 ± 1.55	1.27 ± 1.53	2.64 ± 1.43	.088[a]
Gender					.339[b]
Male	36 (48%)	24 (49%)	5 (33.3%)	7 (63.6%)	
Female	39 (52%)	25 (51%)	10 (66.7%)	4 (36.4%)	
Side					.511[b]
Left	33 (44%)	21 (42.9%)	7 (46.7%)	6 (54.5%)	
Right	42 (56%)	28 (57.1%)	8 (53.3%)	5 (45.5%)	
Neck Length					.310[b]
Short	57 (76%)	39 (79.6%)	9 (60%)	9 (81.8%)	
Long	18 (24%)	10 (20.4%)	6 (40%)	2 (18.2%)	
Bilaterial THA	24 (34.8%)	16 (34%)	7 (58.3%)	2 (18.2%)	.137[b]
Stem size (mm)	4.05 ± 1.54	3.94 ± 1.55	3.73 ± 1.22	5 ± 1.67	.078[a]
Cup size (mm)	54.19 ± 4.30	53.71 ± 4.53	54.67 ± 4.05	55.64 ± 3.44	.368[a]
Liner size (mm)	40.12 ± 6.93	41.4 ± 7.28	37.45 ± 8.49	39.27 ± 2.41	.249[a]
Head length (mm)	1.53 ± 0.77	1.6 ± 0.77	1.27 ± 0.7	1.64 ± 0.81	.316[a]
Head size (mm)	39.38 ± 5.78	40.86 ± 5.89	34.29 ± 4.36	39.27 ± 2.41	.001[a]
Neck angle (degrees)					.124[b]
0	29 (38.7%)	19 (38.8%)	3 (20%)	7 (63.4%)	
4	1 (1.3%)	0 (0%)	1 (6.7%)	0 (0%)	
8	33 (44.0%)	22 (44.9%)	7 (46.7%)	4 (36.4%)	
15	12 (16.0%)	8 (16.3%)	4 (26.7%)	0 (0%)	
Cup manufacture					.001[b]
Lineage	9 (12.5%)	5 (41.7%)	4 (8.2%)	0 (0%)	
Conserve	18 (25.0%)	4 (33.3%)	14 (28.6%)	0 (0%)	
Dynasty	45 (62.5%)	3 (25.0%)	31 (63.3%)	11 (100%)	
Thyroid Disease prior to echo	6 (8%)	5 (10.2%)	0 (0%)	1 (9.1%)	.468[b]
Diabetes Mellitus	13 (17.3%)	9 (18.4%)	3 (20%)	1 (9.1%)	.817[b]
Hypertension prior to echo	53 (70.7%)	34 (69.4%)	9 (60%)	10 (90.9%)	.219[b]
Chronic Kidney Disease	4 (5.3%)	2 (4.1%)	2 (13.3%)	0 (0%)	.272[b]
Aspirin Use	30 (40%)	19 (38.8%)	5 (33.3%)	6 (54.5%)	.576[b]

MoM, metal-on-metal, MoC, metal-on-ceramic, MoP, metal-on-poly, BMI, body mass index, CCI, Charlson Comorbidity Index.
[a] Analysis of Variance (ANOVA), alpha = 0.05 as significant.
[b] Fisher Exact Test, alpha = 0.05 as significant.

Appendix Table 2
Comparison of Serum Titanium, Cobalt, and Chromium Concentrations and Cobalt-Chromium Ratios Between Three Bearing Surfaces Combinations.

Variables	Total (n = 75)	MoM (n = 49)	Ceramic (n = 15)	MoP (n = 11)	*P*-Value
Ti early (ngml)	4.43 ± 5.97	3.63 ± 2.93	7.73 ± 11.94	3.45 ± 1.57	.054[a]
Co early (ngml)	3.04 ± 4.56	4.36 ± 5.16	0.52 ± 0.53	0.62 ± 0.95	.002[a]
Cr early (ngml)	2.31 ± 3.84	3.34 ± 4.42	0.4 ± 0.62	0.35 ± 0.3	.005[a]
Co:Cr ratio early	1.7 ± 1.32	1.61 ± 1.28	2.04 ± 1.48	1.69 ± 1.36	.580[a]
Ti (ngml)	3.73 ± 4.68	4.16 ± 5.52	3.4 ± 3.11	2.45 ± 1.63	.538[a]
Co (ngml)	7.23 ± 25.52	11.12 ± 31.52	0.43 ± 0.56	0.56 ± 0.66	.242[a]
Cr (ngml)	3.33 ± 8.05	5.0 ± 9.76	0.51 ± 0.86	0.36 ± 0.29	.070[a]
Co:Cr ratio	1.89 ± 1.58	2.07 ± 1.84	1.44 ± 0.67	1.66 ± 0.92	.395[a]

MoM, metal-on-metal, MoC, metal-on-ceramic, MoP, metal-on-poly, Ti, titanium, Co, cobalt, Cr, chromium.
[a] Analysis of Variance (ANOVA), alpha = 0.05 as significant.

Appendix Table 3
Comparison of Echocardiographic Cardiac Parameters Between Three Bearing Surfaces Combinations.

Variables	Total (n = 75)	MoM (n = 49)	Ceramic (n = 15)	MoP (n = 11)	*P*-Value
LV Ejection Fraction (%)	63.7 ± 7.11	63.71 ± 6.78	63.53 ± 9.03	63.91 ± 6.24	.991[a]
LV strain	19.08 ± 2.64	18.36 ± 2	19.55 ± 3.51	21.3 ± 2.31	.035[a]
Pulmonary Artery Pressure (mmhg)	26.34 ± 7.53	26.47 ± 8.36	25.42 ± 7.09	26.82 ± 3.57	.891[a]
Tricuspid Annular Plane Systolic Excursion (cm)	2.26 ± 0.44	2.29 ± 0.41	2.11 ± 0.55	2.32 ± 0.31	.376[a]
RVS	0.13 ± 0.03	0.13 ± 0.03	0.13 ± 0.02	0.14 ± 0	.851[a]
RVE	0.11 ± 0.03	0.11 ± 0.03	0.1 ± 0.02	0.2 ± 0	.021[a]
Rvtei index cw	0.37 ± 0.14	0.36 ± 0.13	0.43 ± 0.21	0.57 ± 0	.217[a]
Rvtei index td	0.44 ± 0.11	0.43 ± 0.11	0.47 ± 0.06	0.71 ± 0	.036[a]
Lvtei index	0.41 ± 0.14	0.42 ± 0.14	0.32 ± 0.11	0.36 ± 0	.491[a]
Time until ECHO (y)	8.31 ± 2.47	7.38 ± 1.93	11.4 ± 2.31	8.14 ± .81	<.001[a]
sbpat echo	133.67 ± 15.57	132.6 ± 16.59	127.71 ± 10.39	145.64 ± 10.47	.011[a]
dbpat echo	75 ± 10.26	75.16 ± 10.11	72.57 ± 10.85	77.45 ± 10.43	.510[a]
LV size					.598[b]
Normal	71 (94.7%)	46 (93.9%)	15 (100%)	10 (90.9%)	
Mildly Increasing	4 (5.3%)	3 (6.1%)	0 (0%)	1 (9.1%)	
LV wall thickness					
Normal	45 (62.5%)	30 (62.5%)	9 (60%)	6 (54.6%)	
Mildly Increasing	27 (37.5%)	18 (37.5%)	6 (40%)	5 (45.5%)	
LV Diastolic Filling (grade)					.071[b]
0	25 (36.2%)	13 (28.3%)	6 (46.2%)	13 (27.7%)	
1	34 (49.3%)	27 (58.7%)	5 (38.5%)	28 (59.6%)	
2	9 (13.0%)	6 (13.0%)	2 (15.4%)	6 (12.8%)	
3	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	

MoM, metal-on-metal, MoC, metal-on-ceramic, MoP, metal-on-poly, LV, Left Ventricular.
[a] Analysis of Variance (ANOVA), alpha = 0.05 as significant.
[b] Fisher Exact Test, alpha = 0.05 as significant.

Appendix Table 4
Patient Demographics Compared in Patients With High and Low Cobalt.

Variables	Co < 7 (n = 66)	Co > 7 (n = 9)	*P*-Value
Age (y)	57.82 ± 11.73	59 ± 9.62	.648[a]
BMI	33.75 ± 6.4	32.77 ± 6.68	.618[a]
Height (cm)	154.65 ± 31.58	157.93 ± 24.78	.922[a]
Weight (Kg)	112.46 ± 38.58	96.89 ± 34.33	.203[a]
CCI	1.88 ± 1.63	1.78 ± 1.09	.815[a]
Gender			.298[b]
Male	30 (45.5%)	6 (66.7%)	
Female	36 (54.5%)	3 (33.3%)	

Co, cobalt.
[a] Wilcoxon Rank-Sum Test, alpha = 0.05 significant.
[b] Fisher Exact Test, alpha = 0.05 as significant.

Appendix Table 5
Comparison of Serum Titanium, Cobalt, and Chromium Concentrations and Cobalt-Chromium Ratios Between Patients With High and Low Cobalt.

Variables	Co < 7 (n = 66)	Co > 7 (n = 9)	*P*-Value
Ti early (ngml)	4.17 ± 6.22	6.33 ± 3.28	.009[a]
Co early (ngml)	1.63 ± 1.54	13.4 ± 5.97	<.001[a]
Cr early (ngml)	1.42 ± 1.65	8.82 ± 7.77	<.001[a]
Co:Cr ratio early	1.68 ± 1.4	1.87 ± .59	.093[a]
Ti (ngml)	3.17 ± 3.32	8.86 ± 10.27	.002[a]
Co (ngml)	5.95 ± 25.64	18.94 ± 22.77	<.001[a]
Cr (ngml)	2.73 ± 8.09	8.9 ± 5.46	<.001[a]
Co:Cr ratio	1.84 ± 1.57	2.26 ± 1.72	.472[a]

Co, cobalt.
[a] Wilcoxon Rank-Sum Test, alpha = 0.05 significant.

Appendix Table 6
Comparison of Echocardiographic Cardiac Parameters Between Patients With High and Low Cobalt.

Variables	Co < 7 (n = 66)	Co > 7 (n = 9)	*P*-Value
LV Ejection Fraction (%)	63.82 ± 7.16	62.89 ± 7.06	.619[a]
LV strain	19.16 ± 2.75	18.62 ± 1.94	.754[a]
Pulmonary Artery Pressure (mmhg)	26.79 ± 7.54	23.33 ± 7.14	.384[a]
Tricuspid Annular Plane Systolic Excursion (cm)	2.21 ± 0.42	2.58 ± 0.42	.039[a]
RVS	0.13 ± 0.02	0.13 ± 0.04	.916[a]
RVE	0.11 ± 0.04	0.1 ± 0.02	.276[a]
Rvtei index cw	0.38 ± 0.13	0.28 ± 0.12	.178[a]
Rvtei index td	0.45 ± 0.12	0.39 ± 0.07	.283[a]
Lvtei index	0.41 ± 0.15	0.35 ± 0.07	.248[a]
Time until ECHO (y)	8.38 ± 2.43	7.78 ± 2.85	.322[a]
sbpat echo	133.89 ± 16.05	131.33 ± 9.79	.550[a]
dbpat echo	74.75 ± 10.53	77.67 ± 6.74	.443[a]
LV size			1.000[b]
Normal	61 (93.8%)	9 (100%)	
Mildly Increasing	4 (6.2%)	0 (0%)	
LV Wall Thickness			.643[b]
Normal	38 (61.3%)	7 (77.8%)	
Mildly Increasing	24 (38.7%)	2 (22.2%)	
LV Diastolic Filling (grade)			.611[b]
0	22 (36.7%)	3 (33.3%)	
1	28 (46.7%)	6 (66.7%)	
2	9 (15%)	0 (0%)	
3	1 (1.7%)	0 (0%)	

Co, cobalt.
[a] Wilcoxon Rank-Sum Test, alpha = 0.05 significant.
[b] Fisher Exact Test, alpha = 0.05 as significant.