Investigating the effects of metal-on-metal hip implants and circulating cobalt ions on cardiovascular function

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by

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Declaration of authenticity and author's rights.

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

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Previously published material

This thesis contains previously published material from the paper referenced below. The thesis has been authored by the same first author, Mark R. J. Jenkinson. The first author performed the literature review and wrote the paper. Susan Currie and R. M. Dominic Meek assisted with the design of the review, as well as with corrections to the final manuscript as MPhil supervisors. M. Helen Grant, Rothwelle J. Tate and Sandy MacMillan provided advice as well as corrections to the final manuscript.

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Abstract

Metal-on-metal (MoM) hip arthroplasties are known to release metal ions including cobalt into the blood stream. Elevated blood cobalt at levels over 250µg/l have been shown to be a risk factor for developing cardiovascular complications including cardiomyopathy, a need for cardiac transplantation and, in some cases, death. Published case reports document cardiomyopathy in patients with elevated blood cobalt levels below 250µg/l and as low as 13µg/l. Clinical studies have found conflicting evidence of cobalt-induced cardiomyopathy in patients with MoM hips. Global longitudinal strain (GLS) is an echocardiography measurement known to be more sensitive than ejection fraction at diagnosing early cardiomyopathies. The extent of cardiovascular injury, as measured by GLS, in patients with elevated blood cobalt levels has not previously been examined and is the focus of the current study.

Sixteen patients with documented blood cobalt ion levels above 13µg/l were identified from a regional arthroplasty database. They were age and sex matched with eight patients awaiting hip arthroplasty with no history of cobalt implants. All patients underwent electrocardiogram and echocardiogram assessment for signs of cardiomyopathy including left ventricular (LV) dysfunction and cardiac remodelling. Global longitudinal strain (GLS), E/e' ratio (an index for evaluating LV filling pressure), ejection fraction, LV wall thickness, LV end diastolic dimension, LV end systolic dimension and fractional shortening were all assessed.

The patients with MoM hip arthroplasties had a mean time from initial arthroplasty of 15 years and had a mean blood cobalt level of 29µg/l compared to 0.01µg/l in the control group. Echocardiographic analysis showed no difference in either LV end systolic dimension (2.8cm v 3.0cm, (MoM v control) p=0.592) or LV end diastolic dimension (4.7cm v 5.0cm, (MoM v control) p=0.259). Neither was there any difference between ejection fraction (61.5% v 63.7%, (MoM v control) p= 0.564) or fractional shortening (38.9% v 40.1%, (MoM v control) p=0.813). Ventricular wall thickness (1.2cm v 1.0cm, p=0.059) and E/e' ratio (8.0 v 7.8, p=0.771) were also comparable across MoM and control groups and there was no difference in rates of left ventricular or atrial hypertrophy. GLS was significantly reduced in patients with MoM hip arthroplasties compared to those without (-15.2% v -18%, (MoM v control) p= 0.013).

This study has demonstrated reduced cardiac function in the presence of normal ejection fraction as assessed by GLS in patients with elevated cobalt above 13µg/l. As GLS is a more sensitive measure of systolic function than ejection fraction, routine echocardiogram assessment including GLS should be performed in all patients with MoM hip arthroplasties and elevated blood cobalt above 13µg/l. Further work is recommended to assess if these cardiac changes are present in patients with elevated blood cobalt levels below 13µg/l.

Contents

Abbreviations

AF	Atrial fibrillation
ALVAL	Aseptic lymphocyte-dominant vasculitis associated lesion
AML	Acute myeloid leukaemia.
ARMD	Adverse reaction to metal debris
ATP	Adenosine triphosphate
AV	Atrioventricular
BPM	Beats per minute
Ca2+	Calcium
CaMKII-delta	Calcium/calmodulin-dependent kinase II delta
CMP	Cardiomyopathy
CoC	Ceramic-on-ceramic
Co2+	Cobaltous cobalt
DMT1	Divalent metal ion transporter 1
ECG	Electrocardiogram
E/E' ratio	Ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity
EPO	Erythropoietin
EDV	End diastolic volume
ESV	End systolic volume
GG&C	Greater Glasgow and Clyde
GLS	Global Longitudinal Strain
HFpEF	Heart failure with preserved ejection fraction
LVEF	Left ventricular ejection fraction

LV	Left ventricular
Mg2+	Magnesium
MHRA	Medicines and Healthcare Regulatory Agency
mmHg	Millimeters of mercury
MoM	Metal-on-metal
MoP	Metal-on-polyethylene
QEUH	Queen Elizabeth University Hospital
SEM	Standard error of the mean
T2DM	Type 2 diabetes mellitus
THA	Total hip arthroplasty
TRP	Transient receptor potential

Tables

Figures

1. Introduction

1.1 The challenge

The recent controversy over metal-on-metal (MoM) hip arthroplasties has brought the potential toxic effects of cobalt ions to the forefront of medical research (Cohen, 2012). Cobalt is a naturally occurring metal which is present in many foods and has a wide range of uses in medicines, medical implants and dietary supplements. Due to its excellent wear properties, as part of a cobalt chromium alloy, cobalt has long been used in orthopaedic implants such as plates for fracture fixation and as the hard bearing surface on the femoral head of a total hip arthroplasty (THA). These wear properties were central to the development of newer implants with larger articulations which could allow for a more accurate re-creation of the patient's hip anatomy (Hughes et al, 2018). Unfortunately, after millions of these MoM hip arthroplasties had been implanted into patients worldwide it became apparent that they failed earlier and in greater numbers than conventional hip arthroplasties (NJR, 2014). The manner in which they failed, releasing large quantities of metal wear debris into the surrounding tissues and resulting in cobalt and chromium ions in the blood stream, caused concern among clinicians (Haddad et al, 2011). This build-up of metal wear debris caused large, locally destructive lesions around the hip and cases of systemic complications of cobalt ions were published in the literature. Cobalt cardiomyopathy is a known complication of increased systemic cobalt ions although the mechanism of cardiac injury is still unclear.

1.2 Background to metal-on-metal hip arthroplasty

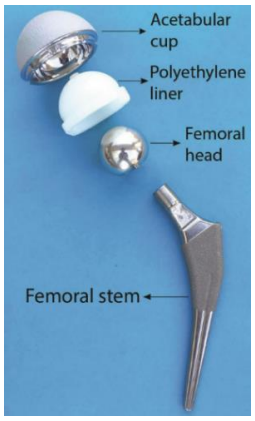


Figure 1: Metal on polyethylene total hip replacement: A photograph of a traditional MoP THA. (Eltit et al, 2016)

Early total hip replacements were comprised of a stainless steel femoral component articulating with a polyethylene acetabulum **(Figure 1)** and despite its rudimentary design, by today's standards, it had a relatively low failure rate and satisfactory longevity (Wrath et al, 2014). When these early hip arthroplasties failed after a few years without the presence of infection it was often due to osteolysis (Karachalios et al, 2018) caused by wear debris activating an inflammatory immune response. A hard femoral head (cobalt chrome or stainless steel) articulating with a softer polyethylene acetabulum causes a large volume of highly biologically active polyethylene wear particles to be released into surrounding tissues leading to osteolysis, aseptic loosening and implant failure.

Figure 2: Large head metal-on-metal hip replacement: A photograph of a large head MoM THA. (Covinsky, 2013)

Highly polished, low friction cobalt chromium MoM implants were developed to reduce the volume of wear particles produced **(Figure 2)**. Early laboratory studies suggested there were 60 times less wear particles produced from MoM hips than from metal-on-polyethylene (MoP) (Cuckler, 2005), reducing the risk of osteolysis. The larger head sizes that this design allowed reduced the risk of dislocation and led to the development of a wide range of implants including hip resurfacing, a bone preserving procedure that replaced the acetabulum and capped the femoral head with cobalt chromium **(Figure 3)**. Unfortunately, after significant numbers of MoM hips were implanted, surgeons started reporting significantly higher revision rates compared to MoP THAs (Drummond, 2015). These observations were confirmed by the national joint registries, national databases of contemporaneously recorded surgical outcomes, who reported failure rates as high as 20%

Figure 3: Metal-on-metal hip resurfacing A photograph of a MoM hip resurfacing (www.mcminncentre.co.uk, 2022)

MoP or ceramic-on-ceramic (CoC) implants (NJR, 2019). At revision surgery it was noted that the tissues surrounding the hip were often stained with metal particles and had associated soft tissue with an unusual appearance. This became known as "Adverse Reaction to Metal Debris" (ARMD). ARMD encompasses a broad spectrum from metal staining (metallosis), through aseptic lymphocyte-dominant vasculitis associated lesion (ALVAL) to a pseudotumour (Watters et al, 2010) and is associated with elevated blood cobalt and chromium ions and systemic cobalt toxicity.

1.3 Cobalt

1.3.1 Cobalt Toxicity

Cobalt is a widespread trace metal found in food, air and water. It is the metallic component of Vitamin B12 and essential for a healthy body, however, excessive levels of cobalt can lead to systemic toxicity. Cobalt can be acutely cytotoxic in larger doses (Simonsen et al, 2012) leading to apoptosis of cells and tissue necrosis with an inflammatory response.

The most common systemic complications involve the neurological system, followed by the cardiovascular system and then the endocrine system (Zywiel et al, 2016). Cobalt toxicity in the heart causes a rapidly progressive cardiomyopathy (CMP) with cyanosis and hypotension (Parker, 2016). Patients can present with severe heart failure and a recent history of anorexia and weight loss and often have predisposing factors including a low protein diet, thiamine deficiency or hypothyroidism. Cobalt CMP has a high short term mortality rate but survivors can experience complete cardiac and clinical recovery similar to

systemic neurological and endocrine toxicity once cobalt has been removed from their system (Packer, 2016).

1.3.2 Cobalt cardiomyopathy

Cobalt cardiomyopathy is a dilated cardiomyopathy similar to idiopathic, non-ischaemic cardiomyopathy (Hantsen, 2019) and is diagnosed by demonstration of biventricular dilatation and systolic dysfunction in the presence of elevated blood or tissue cobalt and the subsequent normalization of cardiac structure and function when cobalt levels return to normal (Packer, 2016). Dilated cardiomyopathy is caused by a poorly contracting left ventricle with normal or reduced ventricular wall thickness. On histological examination the individual myocytes are increased in length with a reduced number of contractile myofibrils and increased myocyte nuclear size (Davies, 2000). Cobalt cardiomyopathy is distinguished from idiopathic, non-ischaemic cardiomyopathy by a history of recent weight loss and anorexia and a background of a low protein diet, thiamine deficiency or hypothyroidism. Cobalt cardiomyopathy, in contrast to idiopathic cardiomyopathy, has a rapid onset and progression, presents with severe heart failure and has a high short-term mortality. Survivors, however, experience complete cardiac and clinical recovery (Packer, 2016). The vast majority of cobalt induced cardiomyopathy research has been into left ventricular function with LV ejection fraction being the most commonly quoted measurement of cardiac function. Research using rats (Marsboom et al, 2009) and chickens (Diaz et al, 1994) has demonstrated that cobalt can cause a right ventricular hypertrophy as well. This leads to pulmonary hypertension.

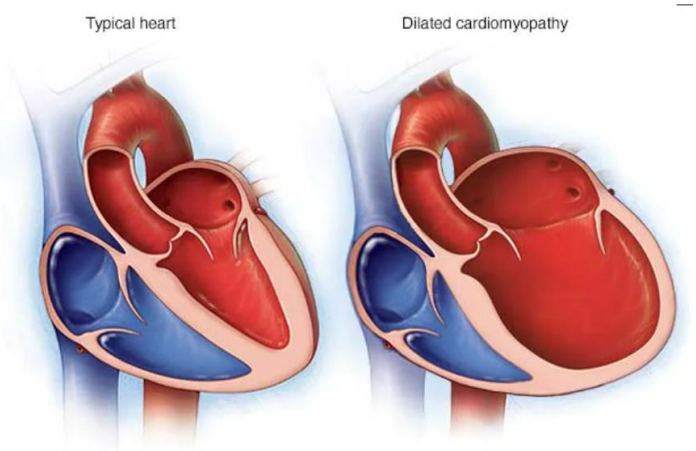


Figure 4: Dilated cardiomyopathy Aclinical illustration demonstrating the difference between an unaffected heart and a heart with dilated cardiomyopathy. (www.mayoclinic.org, 2022)

1.3.3 Mechanism of Action of cobalt on the heart

Cobalt is a heavy metal which forms compounds in 2 forms: Cobaltous (Co^{2+}) and Cobaltic (Co^{3+}) (Leyssens et al, 2017). Co^{2+} is the most common form of cobalt found environmentally and used commercially as the form of cobalt used in MoM THAs.

Cobalt can be both beneficial and damaging to the cardiovascular system. It has a positive effect on the heart in several ways including helping the cardiovascular system respond and adapt to hypoxic stress by mimicking this hypoxic effect. Cobalt enhances erythropoietin (EPO) production, EPO stimulates red blood cell production in the bone marrow. It also increases red blood cell mass and preserves tissue viability during hypoxic stress (Daghmann et al, 1999). It increases expression of hypoxia inducible factor-1 which improves heart function in a low oxygen environment by preventing cell death and encouraging myocardial repair (Simonsen et al, 2012, Xi et al, 2004, Kerendi et al, 2006, Endoh et al, 2000). Cobalt has been shown to induce vascular endothelial growth factor thereby promoting angiogenesis and increases blood flow (Landoux et al, 1994) and it increases activity of glycolysis enzymes which prevent adenosine triphosphate (ATP) depletion by encouraging ATP synthesis in the absence of oxygen (Packer, 2016). It has been shown to form cobalt protoporphyrins which are cytoprotective and anti-inflammatory and have been shown to prevent myocardial and endothelial cell injury (Cao et al, 2012). Cobalt has been shown in laboratory tests on animals to relieve the clinical symptoms of metabolic syndrome, a combination of diabetes mellitus, hypertension and atherosclerotic artery disease by normalizing blood glucose and vascular reactivity (Johns et al, 2009, Saker et al, 1998).

1.3.4 Toxic effects of cobalt on the heart

Excess circulating cobalt can lead to neurological, cardiovascular and endocrine complications (Zywiel et al, 2016). Cobalt toxicity in the heart causes a rapidly progressive cardiomyopathy with cyanosis and hypotension (Packer 2016). The toxic effects of cobalt have been proposed to be due to inhibition of calcium entry, calcium signaling and it's function as a competitor for intracellular calcium binding proteins (Simonsen et al, 2012). The toxic effects of cobalt are reversible as it does not change mitochondrial function (Endoh et al, 2000) or permanently change cardiac contractility (Clyne et al, 1990). Cobalt requires additional factors to increase clinical toxicity, including hypothyroidism and a low

protein, low thiamine diet. Thyroxine, thiamine and cobalt have all been shown to act at the same point of the citric acid cycle (Packer, 2016, Hantsen, 2019).

1.3.4.1 Inhibition of calcium entry

Several proteins dedicated to transporting divalent cations including calcium (Ca2+) and magnesium (Mg2+) into cardiac cells have been considered as the means of Co2+ entering the cells and it has been hypothesized that Co2+ may mimic Ca2+ and use similar transport routes (Laovitthayanggoon et al, 2019). Transient receptor potential (TRP) channels belonging to the TRP superfamily of Ca2+ permeable channels have been suggested as a means of Co2+ entering cardiac cells (Zheng, 2013). Research on TRP proteins has suggested that they can be altered by cobalt to allow it to enter cardiac cells (Monteilh-Zoller et al, 2003, Topala et al, 2007) and that they are present on both contractile and non-contractile cardiac cells (Yue et al, 2015, Rowell et al, 2010). These discoveries led to previous research in our university (Laovitthayanggoon et al, 2019) analyzing whether specific TRP proteins, TRPC6 and TRPM7, and a similar protein, divalent metal ion transporter 1 (DMT1) were responsible for Co2+ uptake into rat cardiac fibroblasts. Results demonstrated that levels of both TRPC6 and TRPM7 were significantly elevated in rat cardiac cells following dosing of animals with cobalt chloride.

1.3.4.2 Inhibition of calcium signaling

Calcium/calmodulin-dependent kinase II delta (CaMKII-delta) is a cardiac protein that is activated early in many forms of heart disease and plays a pivotal role in the pathogenesis of cardiomyopathy (Zhang et al, 2019, Khoo et al, 2006). CaMKII-delta actively regulates pro-inflammatory signaling pathways contributing to pathologic cardiac remodeling (Rusciano et al, 2019) and animal studies have demonstrated that inhibition of CaMKII-delta restores contraction and relaxation in cardiac muscle (Daniels et al, 2018). Increased CaMKII-delta activity has been observed in pathological cardiac processes which result from dysregulation of Ca2+ homeostasis (Wu et al, 2018). This may suggest that CaMKII-delta could be a potentially useful biomarker to detect cardiac dysfunction in patients with elevated circulating cobalt levels prior to clinical or echocardiographic changes.

1.3.4.3 Competition for intracellular calcium binding proteins

Cobalt in the Co2+ form is a divalent cation similar to Ca 2+ and it has been shown to interfere with the binding of calcium at the sarcolemma and transport of Ca2+ into the

myocyte. This ultimately reduces the inotropic effects of Ca2+ (Harrow et al, 1978, Kleinfeld et al, 1968). Cobalt interrupts the citric acid cycle and the generation of ATP by aerobic cellular respiration (Packer, 2016) while also inhibiting the activity of respiratory chain enzymes and ATP production in mitochondria (Clyne et al, 2001) producing a net result of depressing cardiac function and changing cardiac cell structure (Haga et al, 1996)

1.3.4.4 Summary of cobalt cardiotoxicity

A recent review article examined the evidence for a link between elevated blood cobalt levels secondary to MoM hip arthroplasties and cardiomyopathy (Jenkinson et al, 2021). Correlation between low, moderate and high blood cobalt with cardiovascular complications was considered. Elevated blood cobalt at levels over 250µg/l were shown to be a risk factor for developing systemic complications and published case reports document cardiomyopathy, cardiac transplantation and death in patients with severely elevated blood cobalt ions. All deaths in the published literature are in patients with cobalt levels above 200µg/l. However, it is not clear if there is a hard cut off value and cardiac dysfunction may occur at lower levels. Clinical and laboratory research has found conflicting evidence of cobalt induced cardiomyopathy in patients with MoM hips. Studies using registry data to analyse whole populations of patients have demonstrated reduced cardiac ejection fraction on echocardiogram (Prentice et al, 2013)and an increase in cardiac complications in patients with MoM hip arthroplasties compared to non-MoM implants (Gillam et al, 2017, Lassalle et al, 2018). Other studies have failed to demonstrate negative cardiac effects in patients with elevated blood cobalt levels or across populations of MoM hip patients (Lodge et al 2018, Berber et al, 2017, van Lingen et al, 2013, Goodnough et al, 2018, Sabah et al, 2018). These inconsistencies in the knowledge base, as documented in the next section, were the inspiration for this project to clarify the link between severely elevated blood cobalt ions and cardiomyopathy.

1.3.5.1 History of effects of cobalt on the heart

Cobalt cardiomyopathy was first described at a March 1965 cardiology conference in Belgium (Kesteloot, et al, 1968) and the first reported cases in the English literature appeared in the Canadian Medical Association Journal in 1967 (Morin et al, 1967) when a series of 48 Quebec beer drinkers were reported to have developed acute cardiomyopathy after cobalt was added to their beer of choice. A death rate of 41.6% was reported. The authors noted that even large quantities of beer contained much less cobalt than regularly

prescribed nutritional supplements and made the observation that the individual patient's length of alcohol excess prior to exposure to cobalt was a bigger predictor of a fatal outcome than the actual dose of cobalt to which they were exposed (Morin et al, 1967), Mercer et al performed a retrospective review of these patients and found the only universal symptom of cobalt cardiomyopathy present in the Quebec beer drinkers was acute dyspnea (Mercier et al, 1967). Following non interventional treatment none of the survivors examined demonstrated any signs of cardiac failure.

Cobalt cardiotoxicity has also been reported in beer drinkers in Minneapolis, USA who presented with symptoms of cardiomyopathy (Alexander, 1972), a 17-year-old girl on cobalt supplementation receiving haemodialysis (Manifold et al, 1978) and a 48-year-old man with who had suffered cardiogenic shock during a routine operation (Kennedy et al, 1981) following occupational exposure to cobalt.

1.3.5.2 Cardiomyopathy associated with MoM arthroplasty, case reports

Cobalt induced cardiomyopathy secondary to cobalt chrome hip arthroplasties has been described in case reports **(Table 1)** which have been shown to correlate blood cobalt levels with cardiovascular complications (Gessner et al, 2019) and mortality. An analysis of the published case reports available in 2014 found that 10 patients had systemic complications attributable to elevated cobalt and all 10 had blood cobalt levels above 250µg/l (Bradberry et al, 2014). Another review of the medical and toxicology literature suggested a cut off level for blood cobalt of 300µg/l above which otherwise healthy individuals risk developing serious systemic complications (Paustenbach et al, 2014). Patients with nutritional deficiencies such as a hypoalbuminaemia were still at risk of systemic complications below 300µg/l **(Table 2).**

Cases of cobalt induced cardiomyopathy have been reported from primary MoM hip arthroplasties, revision MoM arthroplasty and revision MoP hip arthroplasties following a fracture of a ceramic articulation. Patients have presented between 2 months and 10 years post-operatively with a range of cardiac symptoms including dyspnoea, heart failure, orthopnoea, fatigue and cardiomegaly. Blood cobalt levels have also varied greatly, with symptomatic patients having a serum cobalt level as low as 13µg/l and as high as 6521µg/l. Echocardiographs most commonly demonstrate a decreased left ventricular ejection fraction but have also shown a dilated atrium, diastolic dysfunction, left ventricular hypertrophy and a pericardial effusion. Outcomes have varied from full recovery after

revision surgery or chelation therapy, left ventricular assist device implantation to cardiac transplantation or death (Jenkinson et al, 2021).

The earliest cases of cobalt toxicity secondary to MoM hip arthroplasties were reported in 2010 in Anchorage, Alaska (Tower 2010, 2012, McLoughlin 2010). A previously fit 49 year old man with a normal preoperative echocardiogram developed neurological symptoms following a MoM hip resurfacing. An echocardiogram prior to revision at 43 months post primary surgery demonstrated diastolic dysfunction and his serum cobalt level at this time was 122µg/l. His symptoms resolved following revision of his MoM implant which was accompanied by a reduction in his serum cobalt to 14µg/l.

Cases of cobalt induced cardiomyopathy have been described in patients with large head MoM hip replacement as well as in MoM hip resurfacing. (Mao et al, 2011). Cobalt induced cardiomyopathy has been reported in patients who have undergone MoP hip arthroplasties following a fractured ceramic bearing surface. Ceramic is harder than cobalt chromium and when ceramic fragments get into a MoP or MoM articulation it can lead to rapid failure with a massive release of metal debris and significantly elevated cobalt ions (Zywiel et al, 2013, Choi et al, 2019).

Patients have presented between 2 months (Oldenburg et al, 2009) and 10 years post-operatively (Moniz et al, 2017) at all ages. Dyspnoea is the most common presenting symptom, being mentioned in half of the published case reports **(Table 1).** Other cardiac symptoms include heart failure (Samar et al, 2015), orthopnoea (Tilney et al 2017) and fatigue (Harris et al, 2015). Echocardiograms most commonly demonstrate a decreased left ventricular ejection fraction (LVEF) (Allen et al, 2014). Echocardiograms have also shown a dilated atrium (Machado et al 2012), diastolic dysfunction (Tilney et al, 2017), left ventricular hypertrophy (Peclova et al, 2012) and a pericardial effusion (Zywiel et al, 2013). Outcomes have varied from full recovery after revision surgery, chelation therapy or implantation of a left ventricular assist device to cardiac transplantation or death. Revision surgery to a non-MoM implant has led to a full recovery in almost half of the published case reports (Tower 2010, 2012, McLoughlin 2010) (Machado et al, 2012). Cardiac transplantation was required when the link between MoM implants and cardiomyopathy was missed (Allen et al, 2014) (Moniz et al, 2017) and in patients presenting in extremis with cardiogenic shock (Sans et al, 2019). Chelation therapy can be used as bridging treatment until revision surgery can be performed (Kim et al, 2016) or as a potentially

Cardiac presentation	Implant	Sample	Cobalt (µg/l)	Length of follow up	Echocardiogram results	Outcome
Dyspnoea, neurotoxicity (Tower 2010, 2012, McLoughlin 2010).	Primary MoM arthroplasty	Serum	122	18 months	Diastolic dysfunction	Revision, symptoms resolved
Dyspnoea (Tower 2010, 2012, McLoughlin 2010).	Revision MoM arthroplasty	Serum	23	43 months		Revision, symptoms resolved
Dyspnoea, chest pain (Machado et al, 2012)	Primary MoM arthroplasty	Serum	13	6 years	Dilated atrium, decreased LVEF (21%)	Revision, LVEF (45%)
Exertional dyspnoea, cough (Allen et al, 2014)	Primary bilateral MoM resurfacings	Serum	287	4 years	Decreased LVEF (10%)	Heart transplant, hip revision
Cardiomyopathy (Pelclova et al, 2012)	Failed CoC revised to MoM	Serum	506		Left ventricular hypertrophy	Chelation therapy, revision, symptoms improved
Dyspnoea (Mao et al, 2011)	Primary MoM resurfacing	Serum	258	3 years		Revision surgery, symptoms resolved
Exertional chest tightness, fatigue (Mosier et al, 2016)	Primary bilateral MoM arthroplasties	Whole blood	189	11 months	Decreased LVEF (30%)	Heart transplant, bilateral hip revisions
Dyspnoea (Martin et al, 2015)	Primary bilateral MoM arthroplasties	Did not specify	200- 300	2 years	Decreased LVEF (10-15%)	Death
Fatigue (Zyweil et al, 2013)	Failed CoC revised to MoP	Whole blood	6521	6 months	Pericardial effusion	Death
Dyspnoea, fatigue (Choi et al, 2019)	Failed CoC revised to MoP	Serum	489	6 years	Left ventricular hypertrophy, pericardial effusion, decreased LVEF (13%)	Chelation, revision normal LVEF (58%).
Dyspnoea, orthopnea (Choi et al, 2019)	Failed CoC revised to MoP	Serum	112	6 years	Decreased LVEF (24%), pericardial effusion	Revision surgery, chelation, heart transplantation
Cardiogenic shock (Sanz Perez et al, 2019)	Failed CoC revised to MoP	Serum	652			Heart transplant
Cardiomyopathy (Oldenburg et al, 2009)	Failed CoP revised to MoP	Serum	625	2 months	Left ventricular hypertrophy	Revision surgery, symptoms resolved

Dyspnoea (Fox et al, 2016)	Failed CoC revised to MoP	Whole blood	641	10 months	LVEF 15-20%	Death
Dyspnoea, orthopnoea (Tilney et al, 2017)	MoM	Whole blood	246	4 years	Diastolic dysfunction, decreased LVEF (20%)	Revision surgery, symptoms resolved, LVEF 45-50%
Heart failure (Moniz et al, 2017)	MoM	Serum	169	10 years		Heart transplantation, revision surgery
Exertional dyspnoea (Charette et al, 2017)	Bilateral MoM	Did not specify	156	2 years	Dilated cardiomyopathy with decreased LVEF (20%)	LVAD inserted, no improvement, bilateral hip revisions 1 year later, symptoms resolved
Heart failure (Samar et al, 2015)	Bilateral MoM	Serum	120		Decreased LVEF (36%)	Bilateral revision surgery, LVAD
Heart failure (Khan, 2015)	MoM	Serum	200-300		Decreased LVEF (14%)	Death
Heart failure (Dahms et al, 2014)	Failed CoC revised to MoP	Whole blood	780	2 years	Decreased LVEF (25%)	Chelation therapy, revision surgery, LVEF 40%
Dyspnoea, chest tightness (Vasukutty, 2016)	Failed CoC revised to MoP		45	8 years	Dilated cardiomyopathy, reduced LVEF (28%)	Revision surgery, symptoms resolved
Dyspnoea, fatigue (Gautam et al, 2019)	Failed CoC revised to MoP	Serum	373	3 years	Dilated cardiomyopathy, severe left ventricular dysfunction, LVEF (20%)	Death
Fatigue, tachycardia (Harris et al, 2015)	Failed CoC revised to MoP	Did not specify	788	8 years		Revision surgery, symptoms resolved
Dyspnoea (Kim et al, 2016)	Failed CoC revised to MoP	Did not specify	397		Decreased LVEF (25%)	Cheation therapy, revision surgery, symptoms resolved

Table 1: A Summary of cases reporting cobalt-induced cardiomyopathy
Abbreviations: LVEF, left ventricular ejection fraction; LVAD, left ventricular assist device
Normal values: LVEF 55-70%

curative option (Peclova et al, 2012). Left ventricular assist devices have also been reported as a treatment option (Charette et al, 2017). Five patients have been reported as dying from cobalt induced cardiomyopathy, all five had blood cobalt levels greater than 200µg/l, one had a pericardial effusion on echocardiogram and the other four had LVEF less than 20% at presentation. The mean LVEF at presentation of patients who died was 16% (range, 10-20%) compared to a 21% in cardiac transplant patients (3 patients, range 10-30%) and 23% in those patients whose cobalt induced cardiomyopathy resolved following revision surgery (6 patients, range 13-36%) **(Table 1 and Table 3).**

1.3.5.3 Cardiomyopathy associated with MoM arthroplasty – clinical studies

Due to the large numbers of MoM hip arthroplasties performed, recent clinical studies have tried to determine the risk of cobalt cardiomyopathy posed across the entire population of patients who have received MoM hips **(Table 3).** Lassalle et al identified THAs performed in France between 2008 and 2011 using the French health insurance database. These were separated into MoP, CoP, MoM and CoC and followed up until 2015. All new diagnoses of dilated cardiomyopathy or heart failure in that time were included in the study. Due to the heterogeneity of implants in such a large study they performed 2 separate comparisons. Soft bearing THAs MoP verses CoP and hard bearing implants MoM versus CoC. (Lassalle et al, 2018) They demonstrated a small increase in heart complications in metal hip implants compared to non-metal implants. In contrast Goodnough et al found that there was no increase in cardiac complications in patients with MoM hips. They used the Standards Analytics Files database in the United States to find every patient who had undergone a MoM hip arthroplasty between 2005 and 2012 and compared them to an age and sex matched cohort who had undergone a non-MoM hip arthroplasty in the same period (Goodnough et al 2018). They found that at 5 years there was no difference in cardiac complications such as cardiac failure, arrhythmia, acute myocardial infarction or cardiomyopathy. The limitations of population-based studies such as these are that they are designed to demonstrate epidemiological trends across a heterogenous population without fully exploring the individual subgroups. At best they imply correlation rather than causation. Goodnough's study, in particular, does not answer the question of whether or not certain MoM implants can lead to cardiac complications nor does it seek to answer if elevated levels of cobalt can lead to these problems. A retrospective cohort study of the Australian Government Department of Veterans' Affairs demonstrated that men with an

Blood cobalt levels (µg/l)	Number of patients	Mean/range of blood cobalt levels (µg/l)	Cardiac Presentation	Implants	Echocardiography results	Outcome	References
>250	11	1,049 (258-6521)	Cardiogenic shock (1 case), cardiomyopathy (2 cases), dyspnoea (5 cases), fatigue (4 cases) exertional dyspnoea and cough (1 case),	CoC revised to MoP (7 cases), CoP revised to MoP (1 case), primary MoM resurfacing (1 case), bilateral primary MoM resurfacings (1 case)	Decreased LVEF (5 cases), average LVEF reported was 17% (range 10-25%), Pericardial effusion (2 cases), LVH (3 cases)	Death (27%, 3 cases), Chelation and revision resolved symptoms (27%), Revision resolved symptoms (27%), Heart transplantation (18%, 2 cases)	(Allen et al, 2014, Pelclova et al, 2012, Mao et al, 2011, Zyweil et al, 2013, Choi et al, 2019, Sanz Perez et al, 2019, Oldenburg et al, 2009, Fox et al, 2016, Dahms et al, 2014, Gautam et al, 2019, Harris et al, 2015, Kim et al, 2016)
200-300	2	Unknown	Dyspnoea, heart failure	Primary bilateral MoM resurfacing, Primary MoM resurfacing	Decreased LVEF, average LVEF 13%	Death (100%, both cases)	(Martin et al, 2015, Khan et al, 2015)
<250	10	119.5 (13-246)	Heart failure (2 cases), Dyspnoea (5 cases), exertional chest pain (3 cases) orthopnoea (1 case)	Bilateral primary MoM arthroplasties (3 cases), Primary MoM arthroplasties (4 cases), CoC revised to MoP (2 cases), Revision MoM arthroplasty (1 case)	Decreased LVEF (7 cases), average LVEF reported was 24% (range 10-36%), Diastolic dysfunction (2 cases), Dilated cardiomyopathy (2 cases), Pericardial effusion (1 case)	Heart transplantation and revision (30% 3 cases), Revision resolved symptoms (60% 6 cases), LVAD and revision (10%, 1 case)	(Tower 2010, 2012, McLoughlin 2010, Machado et al, 2012, Mosier et al, 2016, Choi et al, 2019, Tilney et al, 2017, Moniz et al, 2017, Charette et al, 2017, Samar et al, 2015, Vasukutty, 2016)

Table 2: A summary of case reports according to documented blood cobalt level
Abbreviations: LVEF, left ventricular ejection fraction; LVAD, left ventricular assist device
Normal values: LVEF 55-70%

ASR XL hip resurfacing had a statistically significant higher rate of hospitalization for heart failure than men with a MoP THA (Gillam et al, 2017). They did not find this higher rate of complications in women or in men with other types of MoM implants. A retrospective analysis of over half a million hip arthroplasty patients in the United Kingdom's National Joint Registry including 53,529 MoM patients demonstrated no association between a MoM implant and cardiac failure at 7 years post operatively, although the mean age for MoM patients was more than 10 years younger than the non-MoM cohort (Sabah et al, 2018). These studies did not analyse or report blood cobalt levels and they did not seek to explore whether elevated blood cobalt levels were predictive of cobalt induced cardiomyopathy.

Most of the patients who developed cobalt induced cardiomyopathy in the published case reports had significantly raised levels of blood cobalt. Levels above 250µg/l and higher were often associated with the worst cases. Recently published research has attempted to assess patients with as high blood cobalt as possible. Lodge et al recruited 95 patients who had been identified as at risk of MoM complications by having a serum cobalt level of >7µg/l at previous follow up and compared these patients with 15 age and comorbidity matched patients without MoM prosthesis. They rechecked plasma cobalt levels at the time of echocardiogram and divided them into 3 groups. The mean serum cobalt levels in the highest group was 14.6µg/l, 7.8µg/l in the middle group and 1.3µg/l in the lowest, while the control group had a mean plasma cobalt level of 0.6µg/l. They found that increasing cobalt values were associated with increased heart volume but not with cardiac function but the levels of cobalt fell far short of those linked with cobalt induced cardiomyopathy (Lodge et al, 2018).

The London School of Hygiene and Tropical Medicine recruited a total of 90 patients into 3 groups to compare the cardiac function of patients with CoC implants, MoM with low blood ion levels and MoM with elevated blood ion levels (Berber et al, 2017). They found that the mean whole blood ion levels for the 3 groups were 0.17, 2.47 and 30 µg/l respectively and reported that there were no clinically significant findings linking blood ion levels with any cardiac markers. They acknowledge in the discussion of their findings that a mean level of 30 µg/l blood ion levels is elevated but not excessively so which is in keeping with this review of the literature. Likewise, a Dutch team identified the 10 patients in their database of 643 patients with large head MoM hip arthroplasties with the highest cobalt levels.

Reference	Study design	Study group	Control group	Study group blood cobalt µg/l	Findings
Prentice et al (2013)	Cross section associational study	Asymptomatic patients with MoM hip resurfacings	Age and sex matched patients with non-MoM hip arthroplasties	Whole blood cobalt 1.75µg/l compared to 0.38µg/l in control group	Cardiac ejection fraction reduced and end diastolic volume increased in MoM group
Lodge et al (2018)	Single centre, non-randomised, observational study	Patients with MoM hip arthroplasties in 3 groups, separated by cobalt levels	Age matched controls with non-MoM hip arthroplasties	Plasma cobalt in 3 study groups 14.6µg/l, 7.8µg/l and 1.3µg/l compared to 0.6µg/l in control group	Increasing cobalt values associated with increased heart volume but not with cardiac dysfunction and no clinical difference between groups was demonstrated
Berber et al (2017)	Prospective, single centre, blinded trial	MoM bearing with elevated blood cobalt ions	MoM bearing with low blood cobalt ions and CoC bearing	Whole blood cobalt 30µg/l and 2.47µg/l in respective MoM groups compared to 0.17µg/l in control group	No relationship between cobalt levels and ejection fraction. No differences between groups in the left atrial or ventricle size, B-type natriuretic peptide level, or troponin level, and all values were within normal ranges
Van Lingen et al (2013)	Longitudinal cohort study	10 asymptomatic MoM patients with highest cobalt levels out of a population of 643 MoM patients	None	Whole blood cobalt 18-153µg/l (mean 46.8µg/l)	No signs or symptoms of cardiomyopathy could be identified
Gillam et al (2017)	Observational cohort study from Australian Government Department of Veteran's Affairs health claims database	63 men with an ASR XL THA	1,502 men with MoP THA, 199 men with other MoM THAs, 2,044 women with MoP, 58 women with ASR XL THA, 153 women with other MoM THAs	Not recorded	Men with an ASR XL THA had a statistically significant higher rate of hospitalization for heart failure than men with a MoP THA. This higher rate of heart failure was not demonstrated in women or in men with other types of MoM implants

Lassalle et al (2018)	Cohort study in the French National Health Insurance Databases	11,298 patients with MoM hips	93,581 patients with MoP, 58,095 patients with CoP, 92,376 patients with CoC	Not recorded	Small increase in heart complications in metal bearing surfaces compared to non-metal surfaces was identified after controlling for confounding factors, most pronounced in MoM v CoC in women and men over 75 years of age.
Goodnough et al (2018)	Analysis of the Standard Analytics Files database in the United States	29,483 patients with MoM hips	24,175 patients with non-MoM hips	Not recorded	At 5 years there was no difference in cardiac complications such as cardiac failure, arrhythmia, acute myocardial infarction or cardiomyopathy
Sabah et al (2018)	Linkage study between the National Joint Registry, Hospital Episodes Statistics and records of the Office for National Statistics on death	53,529 patients with MoM hips	482,247 patients with non-MoM hips	Not recorded	At 7 years the risk of cardiac failure was lower in the MoM cohort compared with the non-MoM cohort. When the groups were matched their risk of cardiac failure was similar.
Juneau et al (2019)	Cross section study using cardiac magnetic resonance	20 MoM resurfacing patients, 10 bilateral, 10 unilateral	10 case matched non-MoM total hip arthroplasty patients	Mean serum cobalt 1.3µg/l in study group compared to 0.18µg/l in control group	None of the MoM patients showed clinically significant cardiac functional abnormality. The MoM patients had larger end diastolic volumes. There was a small decrease in T2 time in the MoM patients. Higher metal ion levels were associated with larger LV volumes and with shorter T2 time.

Table 3: A summary of published research into cardiovascular complications of metal on metal hip arthroplasties

These patients had a mean whole blood cobalt level of 46.8µg/l, with the highest being 153µg/l. They were followed up for a mean of 4.2 years and none of the 9 women or 1 man demonstrated any signs or symptoms of cardiomyopathy (van Lingen et al, 2013).

Prentice et al (2013) demonstrated that asymptomatic patients with lower levels of circulating cobalt could still suffer cardiac damage, thereby justifying surveillance in all MoM patients. They identified 35 asymptomatic patients with MoM hip resurfacings and 35 age and sex matched patients with conventional non-MoM hip replacements. Echocardiography and blood tests were performed at a mean of 8 years post-surgery. They found that cardiac ejection fraction was reduced and end diastolic cardiac volume was increased in the MoM patients. The blood cobalt level was 1.75µg/l in the MoM group compared to 0.38µg/l in the control group. This study demonstrates that there are measurable differences in cardiac function on echocardiogram in MoM patients without significantly elevated cobalt levels (Prentice et al, 2013). A separate cohort of MoM patients were assessed by cardiac MRI 8 years post operatively and asymptomatic patients with minimally elevated metal ion levels were found to have statistically significant but clinically insignificant mild cardiac changes. This suggests that adverse cardiac processes may be at work in asymptomatic MoM patients, even when they have normal or minimally elevated blood cobalt levels (Juneau et al, 2019).

Researchers have sought to assess for cobalt induced cardiomyopathy at post-mortem. The Mayo clinic selected 75 patients with a history of a cobalt chrome on polyethylene total hip replacement with cardiac tissue available from autopsy and retrospectively analysed it for cobalt levels using plasma mass spectroscopy (Wyles et al, 2017). The results were compared to cobalt levels taken from 73 controls who had no history of metal in their bodies. They found a significantly increased median concentration of cobalt in the myocardial samples of the patients with a history of total hip replacement compared to the control group. A retrospective case series investigating the association between serum cobalt and chromium concentrations and systemic toxicity in MoM patients using 31 consecutive patients referred for tertiary toxicology opinion in London and the United States found only 2 patients with systemic cobalt toxicity, neither had cardiovascular symptoms or cardiomyopathy (Ho et al, 2017).

These studies have not focused on the patient group encountered in the case reports: patients with cardiac failure secondary to cobalt cardiomyopathy with elevated cobalt ions.

Previous authors have analysed the case reports available to them. Paustenbach, et al attempted to define this patient group by cobalt level. They reviewed the medical and toxicology literature to determine a blood cobalt level above which patients developed a risk of serious systemic complications (Paustenbach et al, 2014). After reviewing case reports and case series in both human and animal subjects, investigating neurological, endocrine and haematological as well as cardiac complications, they suggested a cut off of 300µg/l, below which otherwise healthy individuals should not develop complications of systemic toxicity. Below 300µg/l subjects with nutritional deficiencies such as a hypoalbuminaemia were still at risk of systemic complications.

1.4 Assessing cardiotoxicity

1.4.1 Blood Ion levels

Higher metal ion levels reflect a poorly functioning MoM implant (Gunther et al, 2013) with an increased risk of complications (Hailer et al, 2014). Blood cobalt levels of 2µg/l and below reflect a well-functioning hip (Haddad et al, 2011) and the Medicines and Healthcare products Regulatory Agency (MHRA) guidance recommends 7µg/l as a cut-off for clinical concern (MHRA, 2010) (Hughes et al, 2018). This figure was derived from a 2009 study by Hart et al that used data from well-functioning MoM hips and the statistical definition of an outlier (third quartile + 2 × interquartile range) to define a cut-off level of 7 µg/l for cobalt ions in whole blood. This study analysed the effect of cobalt and chromium ions on T lymphocytes and the results were extrapolated to calculate a 90% specificity and 50% sensitivity to predict failure of MoM arthroplasties at these ion levels (Hart et al, 2009). Further studies have attempted to validate this figure and a cut off level of 4µg/l (Nargol et al 2010) and 4.5µg/l (Sidaginamale et al, 2013) have been shown to improve pick up of ARMD but with increased false positives. Implant specific cut-offs have been proposed (Matheru et al, 2016) but the heterogeneity of MoM implants make these an impractical screening tool. Therefore, 7µg/l is still recommended by MHRA to prompt closer follow up and further investigation in the form of cross-sectional imaging (MHRA, 2017).

1.4.2 Cardiac investigation

1.4.2.1 ECG

Cardiological assessment takes the form of ECG and echocardiogram. 12 lead ecgs are performed using 10 electrodes attached to the patient's body. These electrodes are

attached to electrical leads which analyse the electrical activity of the heart from various directions **(Figure 6).** 4 electrodes are attached to the limbs, 1 electrode anywhere on each limb between the torso and the ankle or wrist. 6 electrodes are attached to the torso around the heart. Electrode V1 to the 4th intercostal space to the right of the sternum, V2 to the 4thiIntercostal space to the left of the sternum, V3 to the midway point between V2 and V4, V4 to the 5th intercostal space at the midclavicular line, V5 to the anterior axillary line at the same level as V4 and V6 to the midaxillary line at the same level as V4 and V5. The 4 limb electrodes provide 6 frontal leads that analyse the heart's vertical plane: Lead 1, Lead 2, Lead 3 which analyse the cardiac activity along 3 sides of a triangle formed by the upper limb leads and the left lower limb lead and augmented vector right (aVR), augmented vector left (aVL) and augmented vector foot (aVF) leads which analyse cardiac activity from the centre of the heart to the limbs. The electrode on the right lower limb is a grounding lead which minimizes ECG artifact but does not contribute directly to readings. The 6 chest electrodes, V1 to V6, provide 6 transverse leads which analyse the heart's horizontal plane. Thus the 10 electrodes provide analysis of cardiac activity in 12 directions which allows in depth interpretation of the heart and can localize pathology

1.4.2.2 Normal ECG

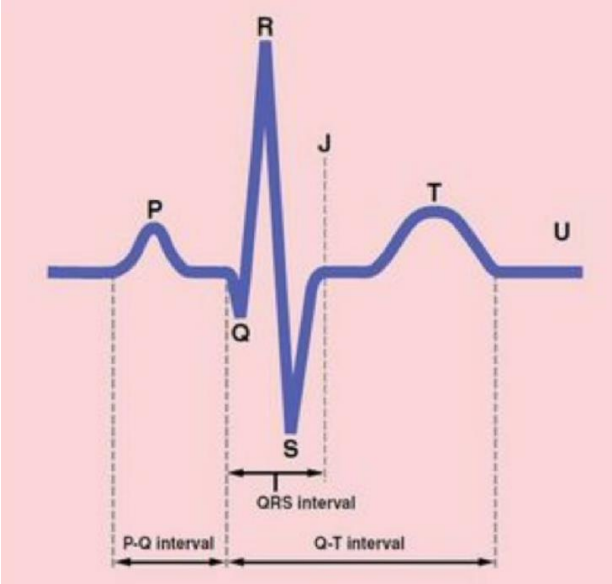


Figure 5: Textbook ecg trace An example of a normal ecg trace showing a p wave which represents atrial contraction, P-Q interval which respresents the time take for the electrical impulse to travel from the atrium to the ventricle, the QRS complex which represents ventricular contraction and the T wave which represents ventricular repolarization. (**www.oxfordmedicaleducation.com**, 2022)

A normal ECG consists of a “P” wave, a “QRS” complex and a “T” wave **(Figures 5 and 7a).** The shape and size of these individual components and their relationship with each other provide clinicians with the information to interpret the ECG. The “P” wave represents atrial depolarization and abnormal p waves are caused by right or left atrial hypertrophy or hyperkalaemia. Irregular “P” waves represent a sinus arrhythmia. The “QRS” complex represent ventricular depolarization and an abnormally wide “QRS” complex is due to a right or left bundle branch block or ventricular rhythm. A “T” wave represents ventricular repolarization and abnormal “T” waves can be taller or smaller than usual, flattened or inverted. Causes of tall “T” waves include myocardial infarction (MI) and left bundle branch block while small, flattened or inverted T waves have a wide range of underlying conditions including ischaemia, pericarditis, pulmonary embolism, certain prescription medications (digoxin), and left ventricular hypertrophy. Intervals between the waves which form part of the ECG assessment are the “PR interval”, the “QT interval” and the “ST segment”. The “PR interval” represents the AV conduction time and is shortened in Wolff-Parkinson-White Syndrome while a lengthened “PR interval” is caused by first degree heart block. The “QT interval” is the time between ventricular depolarization and repolarization and can be lengthened following an MI, or when a patient has myocarditis or hypokalaemia or has had

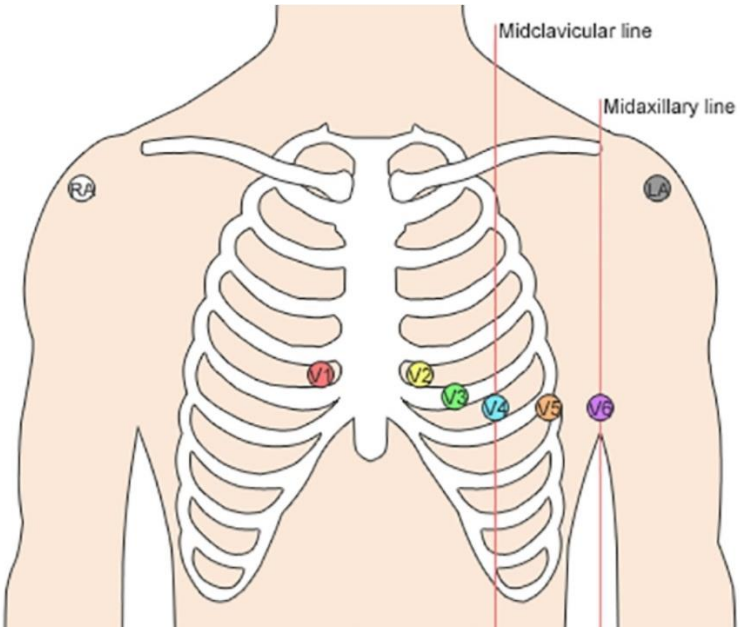


Figure 6: ECG lead placement Lead V1 is placed to the right of the sternum, V2 to the left of the sternum, V4 on the midclavicular line, V6 in the midaxillary line and V3 and V5 midway between V2, V4 and V6.

a subarachnoid or intracerebral haemorrhage. The “ST segment” can be elevated or depressed. “ST segment” elevation can be caused by an acute MI, pericarditis or left bundle branch block. Depression is caused by ventricular hypertrophy, myocardial ischaemia or pulmonary embolis (www.oxfordmedicaleducation.com, 2022).

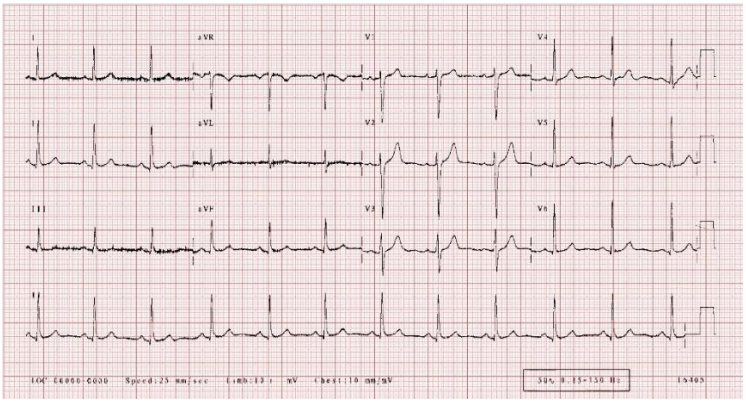


Figure 7a: Normal ECG. An example of a normal ecg trace (www.ecglibrary.com, 2022)

1.4.2.3 Nonischaemic dilated cardiomyopathy ECG

There are no specific ECG changes that are diagnostic of dilated cardiomyopathy. However, when dilated cardiomyopathy is present the ECG can show signs associated with atrial or left ventricular hypertrophy such as “P” wave changes or increased “R” wave amplitude or “S” wave depth. Signs of left bundle branch block such as altered or prolonged “QRS” complex and evidence of left axis deviation can also be present in dilated cardiomyopathy **(Figure 7b).**

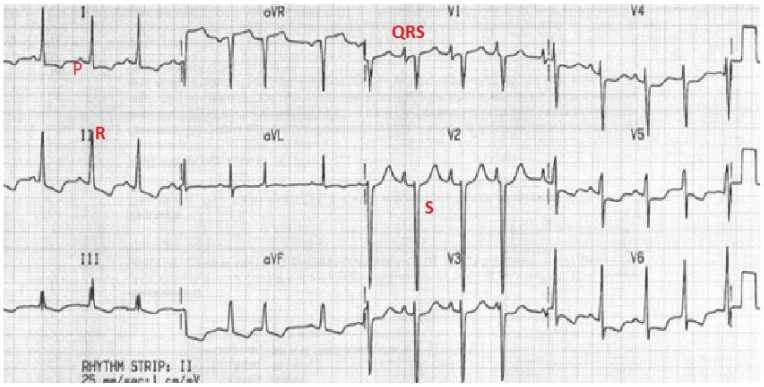


Figure 7b: ECG in non-ischaemic dilated cardiomyopathy. An example of an ecg trace from a patient with non-ischaemic dilated cardiomyopathy with P, R, S waves and QRS complexes labled. (www.ecglibrary.com, 2022)

1.4.2.4 Echocardiogram

Transthoracic echocardiograms are performed by cardiac sonographers and report left ventricular function (systolic and diastolic function), ventricular wall motion and thickness, and analysis of the cardiac valves. Transthoracic echocardiograms assess the heart in 3 planes: Long axis plane, short axis plane and the apical plane. The long axis view **(Figure 8)** provides information on the heart chambers, the mitral and aortic valves, the aortic root and the intraventricular septum. The short axis view can be used to image the entirety of the heart in separate segments, sequentially from cranial to caudal. These views are used to assess all 4 cardiac valves **(Figure 9),** intraventricular septum, pulmonary artery and right ventricular flow. The short axis view also can be used to show left ventricular function, the size of the ventricles, and characteristics of left ventricular hypertrophy. The apical view **(Figure 10)** can be used to show all 4 chambers simultaneously, the mitral and tricuspid valves, the intra-atrial septum, the pulmonary veins and the descending aorta. It can be used to assess contractile function.

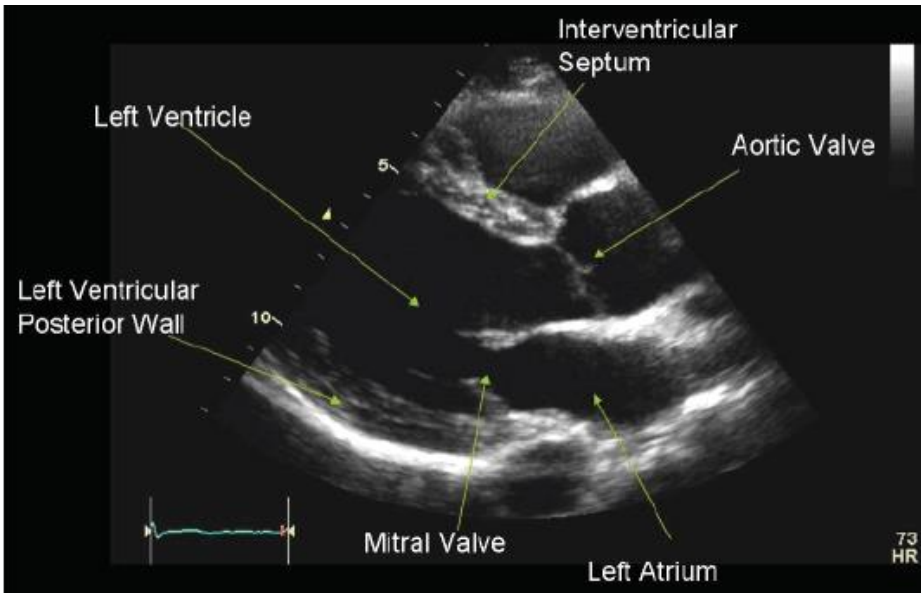


Figure 8: Standard parasternal long axis view An example of an echocardiography image showing the parasternal long axis. (Oxborough, 2008)

1.4.2.5 Echocardiogram measurements

Echocardiography is used to assess patients' left ventricular function. Measurements include left ventricular (LV) ejection fraction, LV end diastolic volume (EDV), LV end systolic dimension, fractional shortening and the E/E' ratio (a ratio of early diastolic mitral inflow

velocity to early diastolic mitral annulus velocity) (Kim et al, 2013). LV ejection fraction is the percentage of blood in the left ventricle ejected with each heartbeat. It is calculated by dividing the stroke volume, the amount of blood leaving the ventricle with each heartbeat, by the end diastolic volume, the maximum amount of blood in the ventricle, and multiplying by 100 to provide a percentage (LVEF= (EDV-ESV)/EDV x 100). LV ejection fraction is considered the central measure of left ventricular systolic function and a value above 50% is considered normal (Kosaraju et al, 2022). As well as contributing to the calculation of ejection fraction, LV end diastolic volume, also known as LV internal diameter (systole) or LIVDs can be increased in dilated cardiomyopathy and increased LV end-systolic dimension was associated with cardiovascular death (Narayanan et al, 2014). Fractional shortening gives an indication as to how well the ventricle is contracting during systole and E/e' ratio is a measure for evaluating the LV filling pressure and is used as a measurement to diagnose diastolic heart failure (Kim et al, 2013).

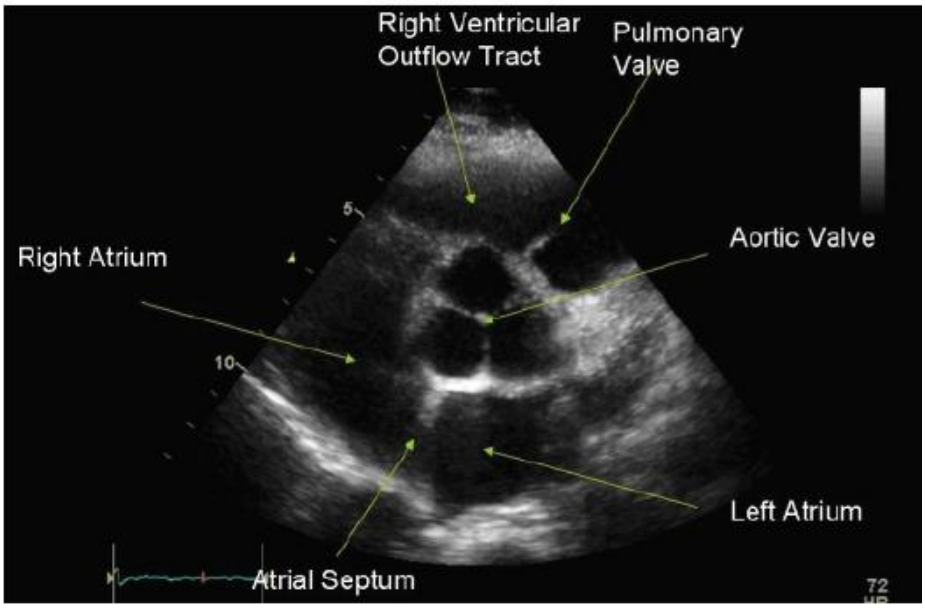


Figure 9: Parasternal short axis view An example of an echocardiography image showing the parasternal short axis. (Oxborough, 2008)

Echocardiography is also used to assess for signs of cardiac remodelling which include Global Longitudinal Strain (GLS), LV end diastolic dimension, LV wall thickness and the overall impression of LV hypertrophy. GLS is a myocardial deformation analysis that predominantly reflects the function of sub-endocardial longitudinally oriented fibres (Joseph et al, 2019) and is used as an alternative to LV ejection fraction to determine systolic function of the heart (Verdonschot, et al, 2021). LV end diastolic dimension, also

known as LV internal diameter (diastole) or LIVDd, measures the size of the LV at the end of diastole as an indicator of LV function and is associated with progressive left ventricular insufficiency (Li et al, 2022). LV wall thickness is one of the measures of LV hypertrophy, an increase in LV mass, which is also recorded by sonographers as a simple conclusion as to whether the patient has LV hypertrophy or not.

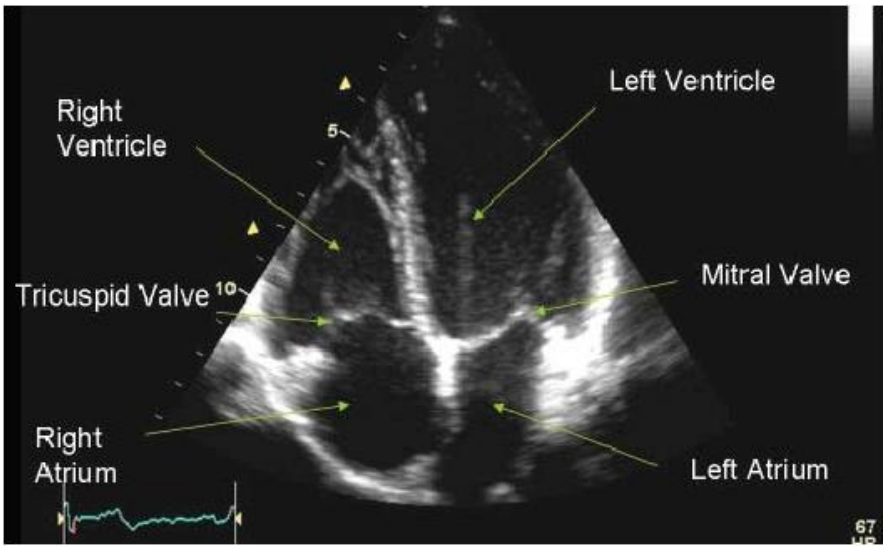


Figure 10: Apical view An example of an echocardiography image showing the Apical view. (Oxborough, 2008)

While LV ejection fraction is the most common reported echocardiography measurement of cardiac function in the cobalt induced cardiomyopathy literature (Jenkinson et al, 2021), GLS has been shown to be more sensitive at picking up cardiac damage in early cardiomyopathies (Verdonschot et al, 2021), Chronic Kidney Disease (CKD) (Krishnasamy et al, 2015) and heart failure (Cho et al, 2009). GLS use is increasing worldwide (Verdonschot et al, 2021) but is not a routine measurement provided by sonographers in Glasgow and the West of Scotland. Therefore, only a small number of sonographers are confident at measuring this important value which has been shown to be sensitive at picking up signs of heart failure in patients presenting with a normal LV ejection fraction.

A normal echocardiogram measures the left atrium, right ventricle, aorta, left ventricle in systole, left ventricle in diastole, the posterior wall, the intraventricular septum and the left ventricular ejection fraction. Dilated cardiomyopathy is diagnosed on echocardiogram by the presence of a dilated left ventricle >112% of expected and a LVEF of <45% (Mathew T, et al, 2017). A normal value for LV ejection fraction is 50% and a normal value for GLS which is given as a negative number is less than -18 (Verdonschot et al, 2021).

1.5 Study Aim

Given the conflicting evidence around the impact of circulating cobalt ions on cardiac function, this project sought to determine whether patients with high circulating levels of blood cobalt show impaired cardiovascular output.

Specific aims included:

1. **To identify a suitable patient cohort for inclusion in the study.**
2. **To undertake blood cobalt measurements and cardiovascular assessments including BP measurements, ECG recordings and echocardiography to measure the effects of elevated blood cobalt on a range of cardiovascular parameters**
3. **To determine whether there are specific measurements that can be used to reflect cobalt-induced cardiac dysfunction and/or remodelling.**

2. Methods

2.1 Metal on metal patient database

The Greater Glasgow and Clyde (GG&C) database of patients who have undergone a MoM hip arthroplasty was used to identify a study group. This database was set up in 2008 when specific complications with MoM implants were first identified. All patients who had undergone a MoM hip resurfacing or large head MoM total hip replacement in the GG&C health board were added to the database and all subsequent patients who continue to receive these implants are added at the time of surgery. It is overseen by a dedicated administrator and an arthroplasty specialist nurse. The patients are followed up as per the Medicines and Healthcare Regulatory Agency (MHRA) guidance with regular blood cobalt levels and clinical and radiological assessments. The database keeps a record of operating surgeon, date and place of surgery, implant make and manufacturer, subsequent surgeries (eg. Revision surgery), imaging results and blood cobalt levels. Any patients with evolving problems are then reviewed by a consultant orthopaedic hip surgeon. Patients with elevated blood cobalt levels are reviewed regularly.

2.2 Study Group Criteria

2.2.1 Inclusion Criteria

Inclusion criteria were male patients over the age of 50 with a blood cobalt level greater than 13µg/l in the past 5 years **(Figure 11)**.

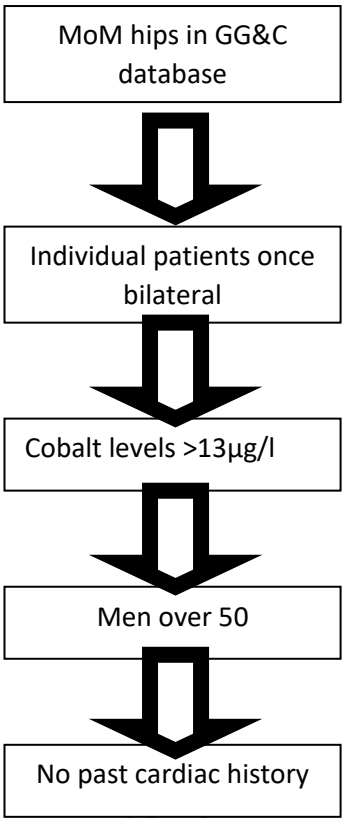
Due to the complications associated with MoM hip arthroplasty the surgical indications have narrowed in recent years and MoM hip resurfacings are now performed in younger, active, male patients with larger femoral head sizes (Haddad et al, 2011)**.** For this research to have ongoing relevance it was therefore decided to limit the study population to men. Cobalt cardiomyopathy has been demonstrated to be more prevalent in patients with significantly elevated blood cobalt levels over 250µg/l (Bradberry et al, 2014), however, early cardiac changes have been demonstrated in asymptomatic patients at levels of blood cobalt as low as 13µg/l (Prentice et al, 2013). As no patients in the GG&C database had blood cobalt levels greater than 250µg/l, the 20 patients with the highest blood cobalt levels, all over 13µg/l, with no previous history of cardiac problems were chosen.

2.2.2 Exclusion Criteria

Exclusion criteria included female patients, men under the age of 50, no history of a blood cobalt level over 13µg/l, revision surgery to remove all MoM arthroplasties and a past medical history of cardiac disease.

This study forms part of a larger, collaborative effort to identify a novel biomarker for early cardiac damage secondary to elevated blood cobalt ions. Patients with a pre-existing diagnosis of cardiac disease were excluded so any cardiac dysfunction identified could be more reliably attributed to their elevated blood cobalt ions. Revision of MoM arthroplasties to non-MoM articulations and associated excision of metallosis, pseudotumour, etc, would prevent further cobalt ions being released into the blood stream and have been shown in the literature to reduce blood cobalt levels. Therefore, patients who have had revision surgery were excluded.

Figure 11: Inclusion criteria Flow diagram demonstrating how patients were selected for inclusion in this study



The patients in the MoM database were stratified by level of blood cobalt ion and the patients with the highest levels were selected **(Figures 11 and 12).** The male patients over the age of 50 with historical blood cobalt levels over 13µg/l were identified from this database and a case note review undertaken to assess for previous cardiac disease. The patients with no recorded history of ischaemic heart disease and the highest blood cobalt level were identified and invited to take part in the study.

2.3 Control Group Criteria

A control group was identified from patients on the waiting list for a primary total hip replacement or hip resurfacing. The inclusion criteria was chosen to match the study group as closely as possible. They were male, over 50 years of age with no past cardiac history. In order to demonstrate that any difference in cardiac function was due to their elevated blood cobalt levels a case note and xray archive review was completed to ensure that they had no history of metal implants. The patients were contacted to provide them with information about the study and confirm that they were happy to attend clinic.

2.4 Ethical Approval

Ethical approval was sought from and granted for this study by the Bloomsbury Research Ethics Committee in London. Approval for a total of 30 patients was sought and granted. Information sheet, consent form and data protection protocols were all included in the application and approved.

2.5 Consenting process

Study participants were contacted by post to inform them of the study and to ask them to consider participating. They were provided with a covering letter and copies of the study information sheet and consent form at this stage. Study participants then attended for review in the orthopaedic outpatient department in the Queen Elizabeth University Hospital (QEUH) in Glasgow. Patients in the study group were reviewed as part of their annual, routine MoM follow up. They had been advised in advance that they would be given the opportunity to enroll in the study. Control group participants were contacted by post informing them of the study and were then contacted by telephone to ask if they were happy to attend a specially arranged clinic appointment at the QEUH.

At these clinic appointments the study was discussed with the patient and a fresh copy of the information sheet was provided to them. Risks and benefits of partaking in the study were discussed and once they had verbally provided their informed consent both the patient and lead researcher signed and dated a consent form.

2.6 Clinical assessment

2.6.1 Clinical history

A thorough history was taken from the patient with regards to their MoM implant. The date of original surgery was confirmed and any complications at the time of surgery were discussed and recorded. The patients were asked if they had had any pain in that hip at any point over the intervening years and if they had had any subsequent radiological investigations or any further operations to that hip. A detailed exploration of current hip symptoms was undertaken including pain and loss of function. Cardiac history was confirmed to be as it had been recorded in the patient case notes and any new cardiac symptoms were explored and documented if present. The patients' past medical history was systematically questioned.

2.6.2 Physical examination

The patients' hips were examined for pain, deformity and reduced range of movement. After an explanation of what the examination entails and informing the patient to alert the researcher to any pain or discomfort the patient was asked to stand and walk the length of the consultation room. Gait patterns were noted and then trendelenbourg test performed to assess for gluteal function. Gluteus medius and minimus function have been shown to be adversely affected by AMRD in poorly functioning MoM hip arthroplasties (Berber et al, 2015b). The patient lay supine on the examination couch and were asked to actively flex and extend their MoM hip. Passive range of movement was examined in flexion, extension, abduction, adduction, internal rotation and external rotation and these movements compared to the contralateral hip. Any restrictions of movement or pain were recorded.

2.6.3 Radiological examination

Anterior-posterior xrays of the pelvis were performed and compared to previous imaging. These were analysed for changes to the MoM implants and the surrounding bone.

Osteolysis around implants and bone loss are the most common initial radiographical findings in AMRD.

2.7 Blood sampling

To analyse these patients for the circulating cardiac biomarkers, blood samples were taken using Tempus™ Blood RNA tubes (Applied Biosystems, UK) to stabilize the RNA in samples intended for gene expression analysis and EDTA containing vacutainer tubes (Becton Dickinson, UK) for protein analysis studies. These samples were transported to the University of Strathclyde where they were stored at -80° degree until required. Blood cobalt levels were measured using an inductive-coupled plasma mass spectrometry technique by the laboratory at QEUH in samples taken at the same time in potassium chloride containing blood vacutainers(Becton Dickinson, UK) designed for trace element analysis.

2.8 Physiological assessment

Patients in both groups had heart rate and blood pressure measured using VS-900 Vital signs Monitor (Mindray, Cambridge, UK) at the same time as blood sampling.

2.9 Cardiological assessment

2.9.1 ECG

Both patient groups underwent 12 lead electrocardiogram (ECG) assessment at the QEUH by trained cardiac physiologists on the same day as their blood sampling. The standard ECG machine used for all ECGs in this study was a GE Mac 5000 (General Electric (GE) Healthcare, Chicago, Illinois, USA)**.** This involved placing four electrodes on the limbs, one electrode anywhere on each limb between the torso and the ankle or wrist. Six electrodes were attached to the torso around the heart. Electrode V1 to the 4th intercostal space to the right of the sternum, V2 to the 4thiIntercostal space to the left of the sternum, V3 to the midway point between V2 and V4, V4 to the 5th intercostal space at the midclavicular line, V5 to the anterior axillary line at the same level as V4 and V6 to the midaxillary line at the same level as V4 and V5.

2.9.2 Echocardiogram

Echocardiograms were performed at a separate appointment using Vivid S70N echo machine (General Electric (GE) Healthcare, Chicago, Illinois, USA) by trained sonographers. Agreement was reached with the sonography department at Glasgow Royal Infirmary for all

echocardiograms to be performed on a single machine by a single sonographer who could provide a measurement of GLS. Due to the pressure on the cardiac physiology department caused by the pandemic this did not happen, instead patients underwent echocardiograms at their local hospital. Echocardiography measurements taken were left ventricular (LV) ejection fraction, LV end diastolic volume, LV end systolic dimension, fractional shortening, E/E' ratio, GLS, LV end diastolic dimension, LV wall thickness and the overall impression of LV hypertrophy. With the exception of GLS, these were all routine echocardiography measurements. LV end diastolic dimension and LV end systolic dimension are also known as LV internal diameter (diastolic) or LVIDd and LV internal diameter (systolic) or LVIDs.

LV ejection fraction is the fraction of chamber volume ejected in systole, otherwise known as the stroke volume, in relation to the volume of the blood in the ventricle at the end of diastole. Stroke volume (SV) is calculated as the difference between end-diastolic volume (EDV) and end-systolic volume. LV ejection fraction is therefore calculated from: LV ejection fraction = [SV/EDV] x 100 (Kosaraju et al, 2023). Echocardiogram imaging systems have a built-in ECG recording system to assist the cardiologist find the end systolic and end diastole frames which are then measured to provide LV end diastolic volume, LV end systolic dimension and LV end diastolic dimension (Darvishi et al, 2013). Fractional shortening is calculated using the measurement of LV diameter taken through the centre point of the LV cavity, during diastole and systole. To calculate fractional shortening of the LV: Fractional Shortening = LVIDd – LVIDs/LVIDd × 100%. Where, LVIDd is the LV internal diameter at end diastole and LVIDs is the LV internal diameter at end systole (Chengode, 2016). E/E' ratio is the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity which is calculated using echocardiogram tissue Doppler velocity (Kim et al, 2013). GLS sentence from paper introduction (Joseph et al, 2019). Left ventricle wall thickness is measured on echocardiography at end diastole (Kinno et al, 2016).

2.10 Statistical analysis

Statistical analysis was performed using Prism-Graphpad (Graphpad Holdings LLC, California, USA). Unpaired t-test was used to compare the mean values of echocardiography findings between the group with elevated blood cobalt and the control group with a p value of less than 0.05 considered significant. Pearson correlation was used to determine if there was a relationship between each echocardiography measurement and

blood cobalt level in the control group with simple linear regression analysis used to assess the significance of these findings.

2.11 Patient consent form

The patient consent form shown on the following page is being used with all patients.

NHS Greater Glasgow

QUEEN ELIZABETH UNIVERSITY HOSPITAL CONSENT FORM
The effect of blood ion levels of Co on biomarkers for cardiotoxicity

PATIENT NAME….....DATE OF BIRTH…....

To be completed by the Patient

Initial		Please Yes	No
. Have you read the Patient Information Sheet (version 1 (06/02/19))?	●	●	
. Have you had an opportunity to ask questions and discuss this study?		●	●
. Have you received satisfactory answers to all your questions?		●	●
. Have you received enough information about the study?		●	●

Who have you spoken to?
Dr/Mr/Ms_____

Do you understand that you are free to withdraw from the study –

.	at any time	●	●
.	without having to give a reason		
.	and without affecting your future medical care?	●	●
Do you agree to take part in this study?		●	●

Do you have any reason to believe you are or may be pregnant?		
	YES, I may be pregnant	●
	NO, I am not pregnant	●

Signed…..... Date…....

Name in Block Letters….....

Signature of Witness…..... Date…....

Name in Block Letters….....

2.12 Patient information sheet

The following patient information sheet is being used with all patients.

Queen Elizabeth University Hospital

Title

Investigating a link between metal hip arthroplasty and altered heart function

Research Question

Can we detect altered levels of a novel biomarker in the blood of patients with hip replacements that informs upon changes in heart function?

Introduction

Metal on metal (MoM) hip arthroplasty was an accepted method of managing arthritic hips in young patients due to the apparent low wear over time. However, it is now known that patients with these hip replacements can show elevated levels of cobalt and/or chromium (the metals used in the bearings of these MoM implants) in blood and urine samples. Over the longer term these metal ions could build up in the organs of the body and, in some cases, might affect patient health. There has been some suggestion of an effect on heart function but this has not been established and it is this we wish to study. We wish to monitor the blood levels of cobalt in patients to investigate whether any changes in heart function of these patients correlates with increased cobalt levels and ultimately with increased levels of a novel biomarker protein called CaM kinase. This protein is very important in heart function. Increased levels and activity of CaM kinase can indicate changes in the structural and functional properties of the heart and can act as an alert before there is any significant compromise in heart function. The possibility that we might be able to identify a biomarker in the blood of patients at an early stage could allow better predictions of whether patients may go on to develop any changes in heart function and therefore allow intervention and prevention of this happening.

Aims and Objectives

The aim of the study is to establish whether there is altered heart function in patients with MoM implants who have high levels of cobalt in the blood. We aim to determine whether any change in heart function and high circulating cobalt levels correlates with increased levels of CaM kinase in the blood in order to understand if this protein could be a useful biomarker.

Ethical Considerations

Confidentiality: Access to patient records and data storage files will be limited to the lead researcher (consultant orthopaedic surgeon named below) and will be stored securely.

Anonymity: Once patients have given their consent to participate, they will be allocated a number which will then be used for all further analysis. No personal information will be known to the wider research team nor will any personal information be used in any presentation of data.

Informed Consent: Informed consent will be obtained on a written consent form by the lead researcher. Prior to gaining consent, patients will be sent a hard copy of the written information sheet, and will have been contacted by phone to allow any initial questions they might have to be addressed. Any further questions will be addressed in person, prior to review.

No ethical issues are envisaged to arise from this study.

A patient information sheet and consent form have been attached.

Supervision

Supervision will be provided by:

Mr R.M.Dominic Meek, MBChB, BSc, MD, FRCS (Tr & Orth), Consultant Orthopaedic Surgeon, SGH

Patient Information Sheet:

Invitation

We would like to invite you to take part in our research study. Joining the study is entirely up to you. Before you decide, we'd like you to understand why the research is being done and what it would involve for you. One of our team will go through this information sheet with you to help you decide whether or not you would like to take part and to answer any questions you may have. You are being asked to participate in a trial to look at whether there may be a link between your hip implant and increased levels of a metal ion called cobalt in your bloodstream. In particular, we wish to establish whether patients with hip implants and high levels of cobalt in their blood may also show changes in the function of their heart and in the levels of a particular protein called CaM kinase. If this is the case, we may be able to use CaM kinase as an early indicator of altered heart function in response to very high levels of cobalt. You should be aware that this research may not be of direct benefit to you but the results of such research may be of benefit to others in the future. Before you decide to take part it is important for you to read the following information carefully and discuss it with friends, relatives and/or your GP if you wish. Please ask us if there is anything that is not clear or if there is anything you would like more information about. Take time to decide whether you wish to participate.

Purpose

It has been shown that very elevated levels of a metal ion called cobalt that may be released from metal-on-metal hip implants may cause changes in heart tissue and function. We are not aware of any problems resulting from these cobalt ions in you. What we wish to establish is whether we are able to detect the presence of a particular protein called CaM kinase in your blood. Research performed by our team and others has shown that this protein is known to be important for cardiovascular health. The levels and activity of CaM kinase can become increased before any changes are obvious in how the heart functions. We therefore believe that CaM kinase might be a very useful biomarker for predicting heart health in patients with hip implants who have high levels of cobalt in their blood. Presence of this protein may enable clinicians to predict whether a patient might go on to develop changes in their heart and allow early intervention to prevent this happening. This work has been funded by Heart Research UK and involves a research team at the University of Strathclyde who are collaborating with the consultant orthopaedic surgeon named above.

Why have you been chosen?

You have been chosen because you have a hip replacement with a cobalt chromium bearing.

Where will the study be conducted?

Blood samples will be taken at the Queen Elizabeth Hospital as part of your routine visit. An electrocardiogram (ECG) or echocardiography measurement may also be taken during your visit. These are non-invasive measurements that allow us to assess heart function and will also be conducted at the Queen Elizabeth Hospital. The ECG involves attaching some small pads to your chest to allow the beating of the heart to be monitored. The echocardiography is a form of ultrasound that allows us to image your heart to visualise any changes and to calculate how efficiently it is pumping blood.

Do you have to take part?

It is entirely up to yourself to decide whether you would like to take part in this study. If you decide to be involved, you will be given this information sheet to keep and you will be asked to sign a consent form. If you decide to participate you are at liberty to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part will not affect the standard of care you receive.

What will happen if you take part?

When you attend for routine review we will request to take some additional blood than what we would normally take (an extra 20 millilitres (4 teaspoons)) to allow us to measure cobalt levels as well as the biomarker in the sample. We may also undertake an ECG and an echocardiogram to look at your heart function. These are non-invasive tests.

Can you participate in the study if you are pregnant?

This research aims to study potential changes or adaptations in the heart following exposure to cobalt. If you are pregnant, your heart will already be undergoing functional adaptations and working harder to provide the increased blood flow required for the foetus. Although the changes that the heart undergoes during pregnancy are completely healthy, they may interfere with any interpretation of changes in heart function we may detect following cobalt exposure. The introduction of this additional significant variable into this particular study may skew the results and for that reason only, we would suggest that you refrain from participation at this time.

What happens if something goes wrong?

This research will not involve any additional invasive procedures as part of your review visit. An extra volume of blood (20 millilitres (4 teaspoons)) will be taken but this will be very quick and within the timing of your usual visit. The factors that might impact upon timing of your visit will be the ECG and echocardiogram which will require an additional 30 minutes of your time. If, in the unlikely event, the ECG or echocardiography readings need to be repeated, the time required might be slightly longer (an additional 20 minutes). This is highly unlikely though as the operator will be highly trained in use of both pieces of equipment and the measurements are relatively quick.

On the day of your review, if you feel that you would rather not participate, you can choose to refrain from providing additional blood or undergoing the ECG and echocardiography. You are not obliged to participate if you feel unwell or unable to travel to the hospital that day. Should unforeseen circumstances in advance of your review appointment preclude you from participating in the study, you can choose to withdraw at any time without supplying a reason.

What do you need to do?

If you choose to take part in the study, there are no restrictions on lifestyle other than that normally associated with already having a total hip replacement.

If you wish to take part in this study then your General Practitioner will be advised of your participation and the clinical management that you will undergo.

What is being tested?

The levels of cobalt ions after a hip replacement are being monitored in blood and correlated with heart function. The levels of a potential protein biomarker called CaM kinase will also be measured in blood samples.

What are the possible disadvantages and risks of taking part?

There are no obvious additional risks to taking part in the study since we aim to incorporate the blood tests and cardiac measurements during your routine visit. The main disadvantage would be an increased length of time for your appointment (increase of approximately 30 minutes). We do not have any information at present to suggest any potential long-term risk from having a metal implant.

What are the possible benefits of taking part?

As with any surgical intervention where something is implanted into the body, the long term effects on overall health should be monitored as carefully as possible. This research aims to provide valuable information on the long term effects of how hip implants might impact upon patients' cardiovascular health. By collecting and analysing this data, benefits may be provided to future hip implant patients. Data from this research will help us understand the long term effects of cobalt on the heart and whether this might impact on hip implant patients' cardiovascular function. Currently we do not know whether there is a link and this will be valuable information for the patient and the clinician. By identifying a potentially useful biomarker, there will be benefits to the clinicians since future routine patient checks could include simple blood tests to ascertain whether a patient may be likely to develop changes in heart function following MoM hip implant surgery. The main benefit though will be to the patient since the possibility of using this biomarker would allow clinicians to intervene and provide treatment to the patient if required and before any significant cardiac changes occur.

If new information becomes available during the trial concerning your treatment then it will be discussed with you.

All information which is collected about you during the course of the research will be kept strictly confidential. The results of this research may be published in scientific journals but no individual will be able to be identified from this. Any samples or information about you, which leave the hospital, will have your name and address removed so that you cannot be recognised from it. The only person with access to your information will be the consultant orthopaedic surgeon at the hospital.

You will be required to sign a consent form to confirm that you understand the information that has been given to you.

3. Results

3.1 Patient details

Patients were identified from the Greater Glasgow and Clyde (GG&C) MoM database and recruited to the study. 2414 MoM hip arthroplasties in 1951 patients are currently being followed up by the GG&C MoM database. 46 patients within the database have recorded a blood cobalt level >13µg/l in the past 5 years. Of these, 25 were men, all 25 of whom were over the age of 50. Following a case note review, 20 of these patients were found to be without pre-existing cardiac conditions. These 20 patients were invited to attend research clinics and offered the opportunity to enroll in the study, 19 of whom accepted. 3 patients later withdrew due to difficulties attending for echocardiograms in Glasgow.

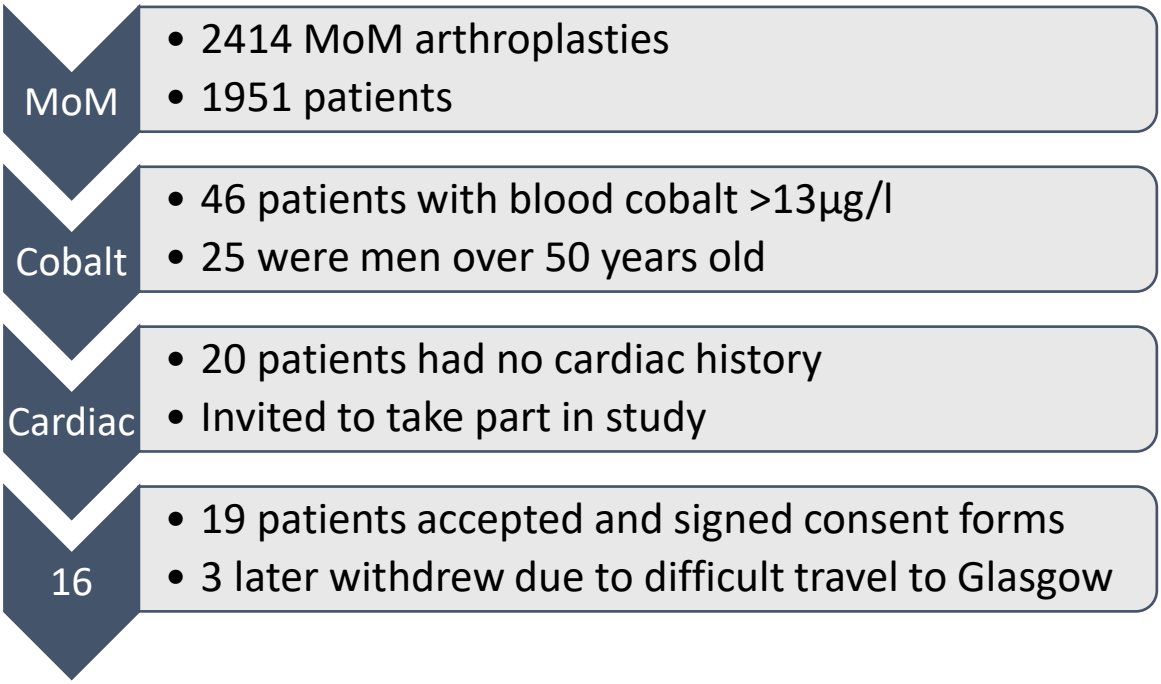


Figure 12: Patient selection A flow chart demonstrating how 16 patients were identified.

The 16 remaining patients were assessed for current medical comorbidities, type of implant and length of time from surgery. 8 patients had a hip resurfacing arthroplasty and 8 had a total hip arthroplasty. The average time from insertion of implant to completion of the study was 15 years which means that no pre-implant patient data was available. 7 out of the 16 patients had no past medical history, 7 had a history of non-cardiac conditions and 2 had developed a cardiac condition between being invited to partake in the study and undergoing echocardiogram. One of these patients had developed hypertension and the

other atrial fibrillation, both patients' conditions were adequately controlled with appropriate medical therapies **(Table 4)**.

Community health index (CHI) numbers are a 4 digit numerical code that when attached to the end of a patient's date of birth provide a 10 digit unique identity number that is used by NHS Scotland to track a patient's health journey throughout their life. They were used as an anonymous way of identifying patients between hospital records and drafts of this thesis. To increase anonymity for the purposes of this thesis these identifiers have been changed to simple letters: A to P for the study group and Q to Y for the control group.

Patient	Age (Years)	Implant	Year of surgery	Medical history
A	71	THA	2007	AF, T2DM
B	61	Resurfacing	2009	Gastric reflux
C	66	Resurfacing	2008	Nil
D	59	THA	2008	Nil
E	68	THA	2008	Nil
F	71	Resurfacing	2004	Nil
G	74	THA	2006	Gout
H	74	THA	2007	Hypertension
I	76	THA	2004	Hiatus Hernia
J	71	THA	2008	Vascular Ulcers
K	83	Resurfacing	2006	Nil
L	67	THA	2008	Diverticulitis
M	68	Resurfacing	2008	AML Prostate cancer
N	82	Resurfacing	2001	Nil
O	61	Resurfacing	2014	Nil
P	69	Resurfacing	2004	Hypercholesterolaemia

Table 4: Study group patient demographics by date of enrollment Patient age is shown at time of enrollment in study, "THA" is total hip arthroplasty, "Resurfacing" is hip resurfacing arthroplasty, "AF" is atrial fibrillation, "T2DM" is type 2 diabetes mellitus, "AML" is acute myeloid leukaemia. n= 16

The patients invited to participate in the study as the control group were identified from the NHS GG&C waiting list. They were male patients over the age of 50 who were waiting for either a total hip replacement or a hip resurfacing arthroplasty with no history of cobalt implants and no prior history of cardiological conditions. 1 patient declined to participate, of the other 9, 4 had no past medical history, 3 had a history of non-cardiac conditions and 2 had developed hypertension, both of which were well controlled using antihypertensive medication **(Table 5)**.

Patient	Age	Medical history
Q	65	Nil
R	77	Sleep Apnoea
S	54	Nil
T	60	Nil
U	60	Ulcerative colitis
V	57	Hypertension
W	60	Nil
X	64	Hypertension
Y	52	Gout

Table 5 Control group demographics Patient age and past medical history. n=9

The average age of the patients in the study group is 70 years old compared to 61 years old in the control group.

In order to confirm a clear difference in circulating blood cobalt levels between the study group and control group, blood cobalt levels were measured using ICP-MS_ The mean blood cobalt level in the study group was 29µg/l compared to 0.01µg/l in the control group (p=0.0002). 8 of the 9 patients in the control group had a cobalt level of 0.0 µg/l and the final patient had a blood cobalt of 0.1µg/l **(Tables 6 and 7)**.

Patient	Age	Blood cobalt (µg/l)
A	71	26
B	61	41
C	66	27
D	59	20
E	68	19
F	71	22
G	74	17
H	74	18
I	76	25
J	71	17
K	83	28
L	67	18
M	68	17
N	82	29
O	61	84
P	69	54

Table 6 Study group patient cobalt levels Blood cobalt micrograms per litre (µg/l). n=16

Patient	Age (Years)	Blood cobalt (µg/l)
Q	65	0.0
R	77	0.0
S	54	0.0
T	60	0.0
U	60	0.1
V	57	0.0
W	60	0.0
X	64	0.0
Y	52	0.0

Table 7 Control group patient cobalt levels Blood cobalt micrograms per litre (µg/l). n=9

The mean blood cobalt level in the study group was 29µg/l compared to 0.01µg/l in the control group (p=0.0002) with standard error of the mean (SEM) ±6.348 **(Figure 13)**.

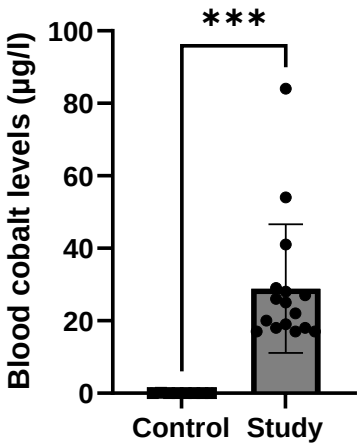


Figure 13: Blood cobalt levels in patient control and stud groups. Histogram showing blood cobalt levels (µg/l) in the control (n=9) and study (n=16) groups. *** represents statistical significance p=0.0002.

3.2 Physiological measurements

In order to determine if there are any differences in cardiovascular parameters between the 2 groups, initial measurements of heart rate and blood pressure were performed. All patients who attended the orthopaedic outpatient department in the QEUH and enrolled in the study had their heart rate and blood pressure measured. Unfortunately, documentation of these measurements by nursing staff was incomplete and 4 out of 16 of the study group and 1 out of 9 of the control group did not have their results available for analysis. There was no statistically significant difference between the 2 groups for either heart rate or

blood pressure. The mean heart rate was 80 beats per minute for the study group compared to 78 beats per minute for the control group (p=0.717, SEM±7.55) **(Figure 14)**, the mean systolic blood pressure was 143mmHg for the study group compared to 152mmHg for the control group (p=0.165, SEM±7.013) **(Figure 16)** and the mean diastolic blood pressure was 81mmHg for the study group compared to 88mmHg for the control group (p=0.179, SEM). The following tables **(Tables 8 and 9)** demonstrate the physiological measurements of the 2 groups.

Patient	Age (Years)	Heart rate (bpm)	Blood pressure (mmHg)
A	71	92	140/82
B	61	77	124/71
C	66		
D	59	90	157/76
E	68		
F	71	70	150/92
G	74	72	162/89
H	74		
I	76	79	160/102
J	71	61	
K	83	94	124/70
L	67		
M	68	71	148/77
N	82	80	123/84
O	61	92	140/82
P	69	77	124/71

Table 8: Heart rate and blood pressure measurements in the study group Heart rate: beats per minute, blood pressure: mmHg. Heart rate n=12, blood pressure n=11

Patient	Age (Years)	Heart rate (bpm)	Blood pressure (mmHg)
Q	65	64	
R	77	93	140/70
S	54		
T	60	60	174/100
U	60	128	161/97
V	57	71	154/82
W	60	60	153/90
X	64	77	148/88
Y	52	68	136/90

Table 9: Heart rate and blood pressure measurements in the patient control group Heart rate beats per minute, blood pressure mmHg. Heart rate n=8, blood pressure n=7

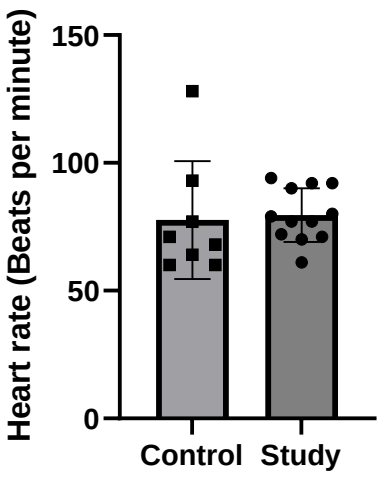


Figure 14: Comparison of heart rate in the patient control and study groups. A histogram showing mean heart rate (beats per minute, (BPM)) in the study group (n=12) compared to the control group (n=8) (p=0.717)

If the control patient with the outlying heart rate of 128bpm is removed from the analysis then the difference between the mean heart rates is 10bpm (80bpm v 70bpm (MoM v Controls) p=0.096, SEM ±5.19) **(Figure 15)**. These heart rate measurements are within the normal values (60 to 100 bpm) expected of men this age.

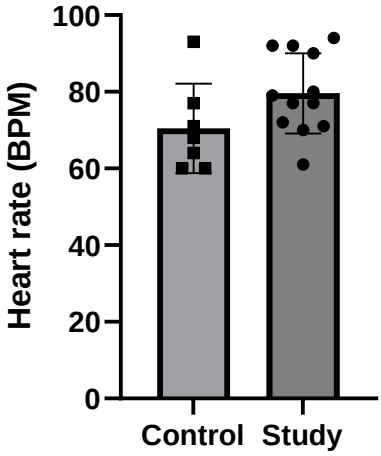


Figure 15: Comparison of heart rate between patient control and study groups when outlier is removed from analysis. A histogram showing mean heart rate (beats per minute) in the study group (n=12) compared to the control group (n=7) (p=0.096)

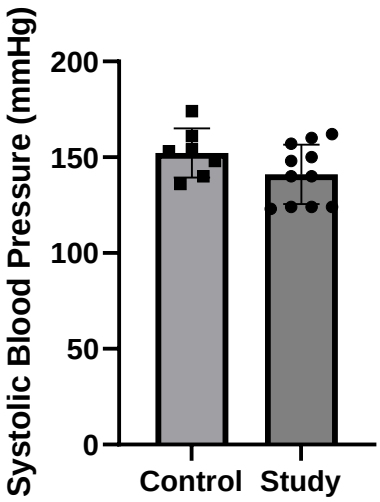


Figure 16: Comparison of systolic blood pressure between patient control and study groups. A histogram showing mean systolic blood pressure (mmHg) in the study group (n=11) compared to the control group (n=7) (p=0.179)

3.3 Electrocardiography (ECG)

Following on from the initial assessment of blood pressure and heart rate the next stage was to perform electrophysiological assessment.

Patient	Age (years)	ECG findings
A	71	Normal sinus rhythm
B	61	Sinus rhythm with premature ventricular complexes
C	66	
D	59	Normal sinus rhythm
E	68	
F	71	Normal sinus rhythm
G	74	1st degree AV block
H	74	
I	76	Normal sinus rhythm
J	71	
K	83	1st degree AV block
L	67	
M	68	Sinus rhythm with premature ventricular complexes
N	82	Sinus rhythm with premature ventricular complexes
O	61	Normal sinus rhythm
P	69	

Table 10 ECG findings in study group. Abbreviation: “AV” is atrioventricular. n=10

First degree heart (AV) block is a split-second delay in the time that it takes electrical pulses to move through the AV node and pass from the atrium to the ventricle. First degree heart block is seen as a slight extension of the gap between p and q waves on an ECG (**Figure 5).** Sinus rhythm with premature ventricular complexes are occasional additional heart beats without atrial activity. These conditions are usually asymptomatic and treatment is rarely required (www.nhsinform.scot). There is no link between these ECG findings and hypertension.

Patient	Age (Years)	Blood cobalt (µg/l)
Q	65	Normal sinus rhythm
R	77	Normal sinus rhythm
S	54	
T	60	Normal sinus rhythm
U	60	Sinus tachycardia
V	57	Sinus bradycardia
W	60	Normal sinus rhythm
X	64	Normal sinus rhythm
Y	52	Sinus rhythm with premature ventricular complexes

Table 11: ECG findings in control group (n= 8)

Ten ECGs are currently available for the study group **(Table 10)** compared to eight available for the control group **(Table 11)**. 50% of the study group have normal sinus rhythm compared to 62.5% of the control group. 20% of the study group had 1st degree heart block compared to none of the control group. 30% of the control group had sinus rhythm with premature ventricular complexes compared to 12.5% of the study group. Examples of ECG traces from the study group **(Figure 17)** and the control group **(Figure 18)** are below.

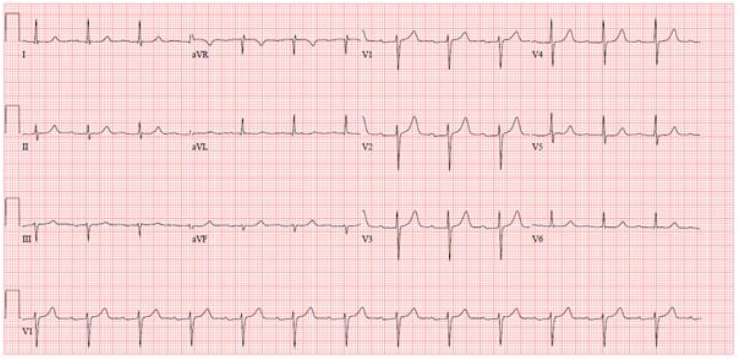


Figure 17: ECG from study group (1st degree AV block) An ecg trace from Patient G

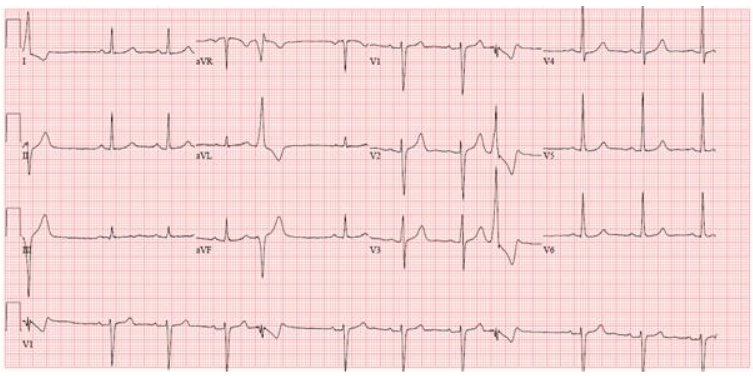


Figure 18: ECG from control group (sinus rhythm with premature ventricular complexes).
An ecg trace from patient Y

3.4 Echocardiogram

In order to assess the cardiac function of the study participants in more detail echocardiograms were arranged. These are routinely performed by sonographers in the cardiology department to assess patients cardiac function. Orthopaedic surgeons and anaesthetists are familiar with interpreting the findings in a peri-operative context, especially when determining if a patient is fit for an orthopaedic operation.

Echocardiograms were arranged for each patient in the study group and the control group. Prior to the Covid-19 pandemic an arrangement with Prof Brady, Consultant Cardiologist and Denise Skedd, Lead Sonographer at the Cardiology Department of Glasgow Royal Infirmary, was made for each patient to undergo their echocardiogram with the same sonographer. This was to standardize the process as much as possible. Unfortunately, due to the pressures on the sonography department, and the entire NHS, caused by the Covid it was not possible for this to happen. 12 sonographers in 6 hospitals performed a total of 20 echocardiograms between the 2 groups. The study group had 12 echocardiograms performed by 11 sonographers in 6 hospitals, Glasgow Royal Infirmary, Stobhill Hospital, the QEUH, the New Victoria Hospital, Royal Alexandria Hospital and Inverclyde Royal Hospital. The additional 4 patients are still awaiting echocardiograms at the time of submission of the thesis. The control group had 8 echocardiograms performed by 3 sonographers in 2 hospitals, Glasgow Royal Infirmary and Stobhill Hospital and 1 patient is still awaiting an echocardiogram. The unavoidable variation in sonographers has led to variation in the parameters measured.

3.4.1 Left ventricular dysfunction

The echocardiograms were used to measure the cardiac parameters which are used to assess for left ventricular dysfunction **(Table 12 and 13)** and cardiac remodeling **(Table 14 and 15)**. A comparison of both groups and summary of means and correlations is also included **(Table 16)**.

Ejection fraction was measured in 6 out of 12 patients in the study group and in all 8 patients in the control group **(Figure 19)**. There was no statistically significant difference between the means. Mean ejection fraction for the cobalt study group was 61.5% compared to 63.7% for the control group (p=0.564, SEM ±3.688) and the difference between the means was 2.2% (95% CI -5.8 to 10.2).

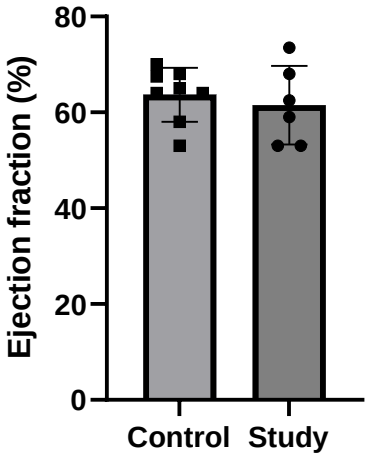


Figure 19: Comparison of ejection fraction between patient control and study groups. A histogram showing mean ejection fraction (%) in the study group (n=6) compared to the control group (n=8) (p=0.5641)

The LV end systolic dimension was available for all patients who underwent an echocardiogram in both groups, 12 in the study group and 8 in the control group. There was no statistically significant difference between the 2 groups **(Figure 20)**. The mean end systolic dimension in the cobalt study group is 2.8cm compared to 3.0cm for the control group (p=0.592, SEM ±0.258) with a difference between the 2 groups of 0.14cm (95% CI -0.4 to 0.7). Pearson correlation of end systolic dimension with cobalt level in the study group was r -0.22 (p= 0.492) and simple linear regression analysis did not show a significant slope (**Figure 21)**.

Patient	Age (Years)	Blood Cobalt (µg/l)	Ejection fraction (%)	LV end diastolic volume (ml)	LV end systolic dimension (cm)	Fractional shortening (%)	E/e' ratio
A	71	26			3.4	32%	8.4
B	61	41	53		2.6	48%	7.1
C	66	27					
D	59	20	68	123	2.1	49%	10.6
E	68	19			2.8	36%	6.5
F	71	22		105	2.1	55%	5.6
G	74	17			3.2	27%	9.3
H	74	18					
I	76	25		98	2.8	39%	8.2
J	71	17	74	62	2.4	37%	
K	83	28			3.6	31%	7.4
L	67	18					
M	68	17	63	78	3.6	31%	8.2
N	82	29	59	158	2.6	54%	8.8
O	61	84	53	102	3.3	28%	
P	69	54					

Table 12 Echocardiogram values for study group Abbreviations: "LV" is left ventricular. Ejection fraction n=6, LV end diastolic volume n=7, LV end diastolic dimension n=12, fractional shortening n=12, E/e' ratio n=2.

Patient	Age (Years)	Blood cobalt (µg/l)	Ejection fraction (%)	LV end diastolic volume (ml)	LV end systolic dimension (cm)	Fractional shortening (%)	E/e' ratio
Q	65	<1	70	152	3.7	34%	6.3
R	77	<1	68		2.2	53%	4.8
S	54	<1	68	113	2.4	51%	6.2
T	60	<1	53	157	2.3	59%	9.8
U	60	0.1	58	94	3.2	30%	7.5
V	57	<1					
W	60	<1	64	131	3.3	38%	10.9
X	64	<1	65	71	2.9	28%	8.2
Y	52	<1	64	141	3.9	28%	8.5

Table 13 Echocardiogram values for control group Abbreviations: "LV" is left ventricular. Ejection fraction n=8, LV end diastolic volume n=7, LV end diastolic dimension n=8, fractional shortening n=8, E/e' ratio n=8

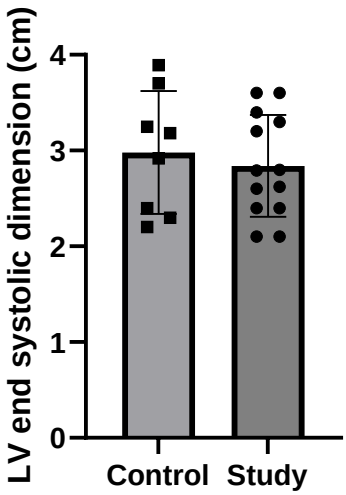


Figure 20: Comparison of LV end systolic dimension between patient control and study groups. A histogram showing mean LV end systolic dimension (cm) in the study group (n=12) compared to the control group (n=8) (p=0.592)

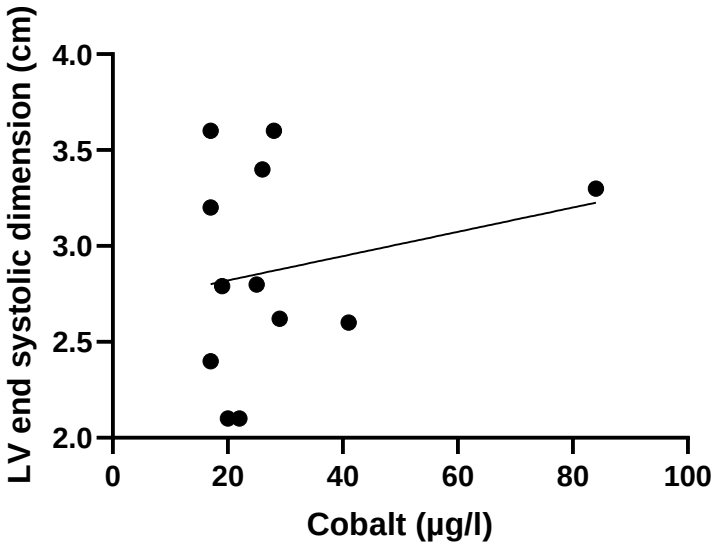


Figure 21: Correlation of LV end systolic dimension with cobalt levels Simple linear regression analysis correlating LV end systolic dimension with blood cobalt levels. (n=12)

Fractional shortening was available for all patients who underwent an echocardiogram in both groups, 12 in the study group and 8 in the control group. There was no statistically significant difference between the 2 groups **(Figure 22)**. The mean fractional shortening for the cobalt study group was 38.9% compared to 40.1% for the control group (p=0.813, SEM ±5.041) and the difference between the 2 groups was 1.2 (95% CI -9.4 to 11.8). The Pearson

correlation of fractional shortening with cobalt level for the study group was r 0.39 (p=0.235) and simple linear regression analysis did not show a significant slope **(Figure 23)**.

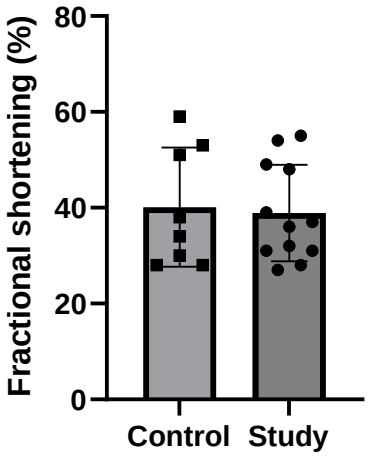


Figure 22: Comparison of fractional shortening between patient control and study groups. A histogram showing mean fractional shortening (%) in the study group (n=12) compared to the control group (n=8) (p=0.813)

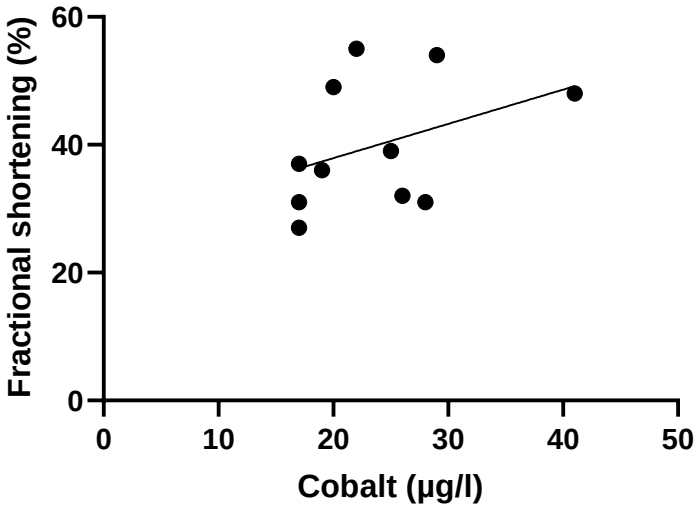


Figure 23: Correlation of fractional shortening with cobalt levels Simple linear regression analysis correlating of fractional shortening with blood cobalt levels. (n=12)

The E/e' ratio was available for 10 patients out of 12 who had undergone an echocardiogram in the study group and all 8 who had undergone echocardiogram in the control group. There was no statistically significant difference between the 2 groups **(Figure 24)**. The mean E/e' ratio for the cobalt study group was 8.0 compared to 7.8 in the control group (p=0.771, SEM ±0.809) and the difference between the 2 groups was -0.2 (95% CI -2

to 1.5). The Pearson correlation of E/e' ratio with cobalt level in the study group is r -0.22 (p=0.534) and simple linear regression analysis did not show a significant slope **(Figure 25)**.

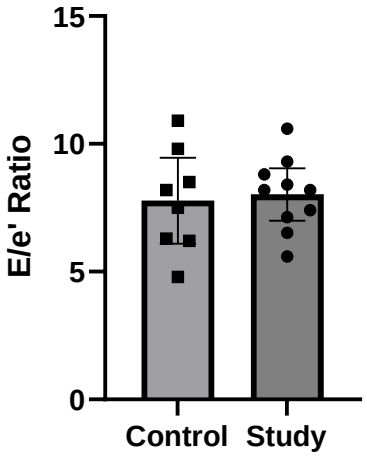


Figure 24: Comparison of E/e' ratio between the patient control and study groups. A histogram showing mean E/e' ratio in the study group (n=10) compared to the control group (n=8) (p=0.771)

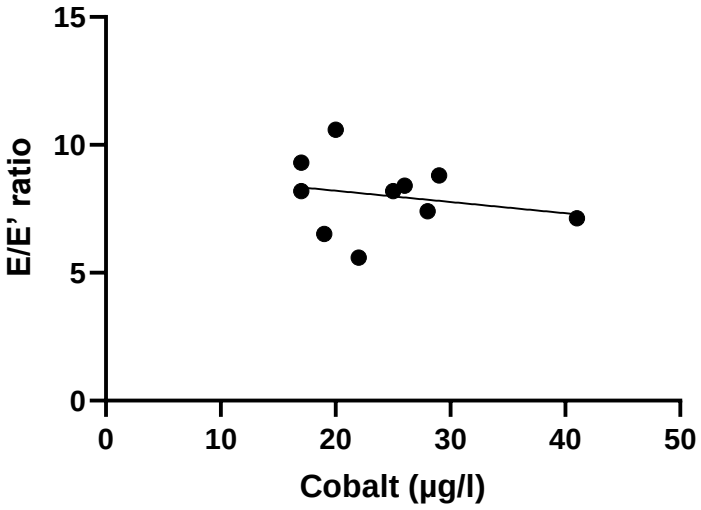


Figure 25: Correlation of E/e' ratio with cobalt levels Simple linear regression analysis correlating E/e' ratio with blood cobalt levels. (n=10)

LV end diastolic volume was calculated in 7 out of 12 patients in the study group and 7 out of 8 in the control group **(Figure 26)**. The mean LV end diastolic volume was 103.7 ml in the study group compared to 122.7ml in the control group (p=0.279, SEM ±16.75). The Pearson

correlation for LV end diastolic volume with cobalt level in the study group was r 0.12 (p=0.790) and simple linear regression analysis did not show a significant slope **(Figure 27)**.

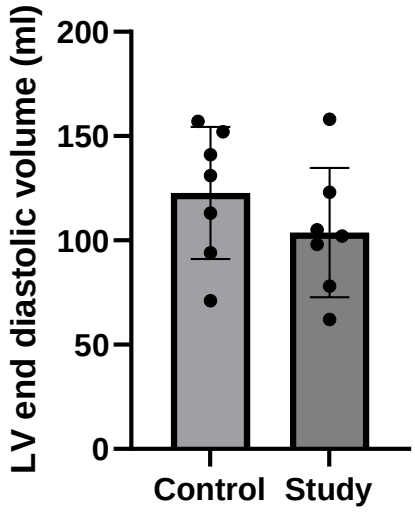


Figure 26: Comparison of LV end diastolic volume between the patient control and study groups. A histogram showing mean LV end diastolic volume in the study group (n=7) compared to the control group (n=7) (p=.2789)

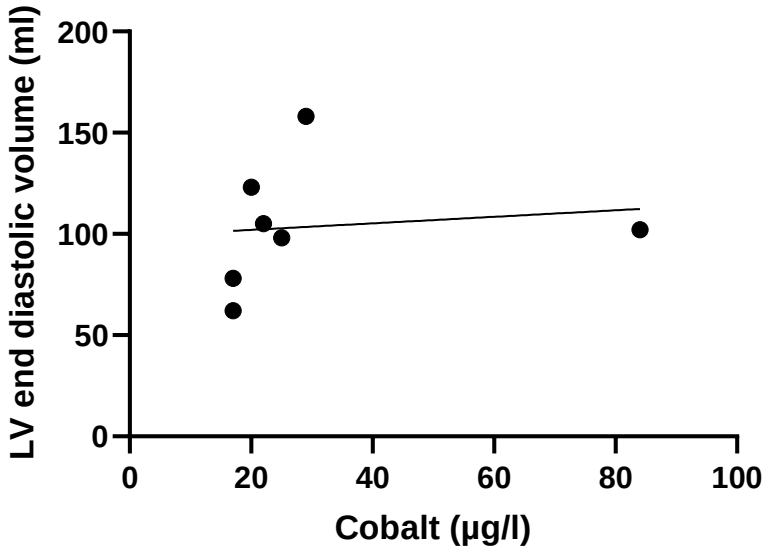


Figure 27: Correlation of LV end diastolic volume with cobalt levels. Simple linear regression analysis correlating LV end diastolic volume with blood cobalt levels. (n=6)

3.4.2 Cardiac remodeling

In addition to the measures of LV dysfunction presented above, the echocardiograms were used to assess for signs of cardiac remodeling in the study group **(Table 14)** and in the control group **(Table 15)**. A comparison of both groups and summary of means and correlations is also included **(Table 16)**.

Patient	Age (Years)	Cobalt (µg/l)	Global longitudinal strain (%)	LV end diastolic dimension (cm)	Wall thickness (cm)	?Left ventricular hypertrophy
A	71	26		5.0	1.0	No
B	61	41	-13.4	5.0	1.2	Yes
C	66	27				
D	59	20	-16.5	4.1	1.5	No
E	68	19		4.4	1.0	No
F	71	22		4.7	1.0	No
G	74	17		4.4	1.4	Yes
H	74	18				
I	76	25		4.6	1.1	No
J	71	17		3.8	1.0	No
K	83	28		5.2	1.2	No
L	67	18				
M	68	17		5.2	1.1	No
N	82	29	-17.3	5.7	1.1	No
O	61	84	-13.4	4.6	1.2	Yes
P	69	54				

Table 14: Echocardiogram values for study group

Patient	Age (Years)	Blood cobalt (µg/l)	Global longitudinal strain (%)	LV end diastolic dimension (cm)	Wall thickness (cm)	?Left ventricular hypertrophy
Q	65	<1		5.6	0.9	No
R	77	<1	-18.5	4.7	1.3	Yes
S	54	<1		4.9	0.9	No
T	60	<1	-16.9	5.7	1.2	No
U	60	2	-18	4.5	0.9	No
V	57	<1				
W	60	<1	-18.7	5.2	0.9	No
X	64	<1	-18	4.0	1.0	No
Y	52	<1	-17.6	5.4	1.0	No

Table 15: Echocardiogram values for control group

GLS was available for 4 of the 12 patients in the study group who had undergone echocardiogram. Of the other 8 patients, 4 had their echocardiograms performed in departments which do not measure GLS and the other 4 patients the sonographer documented that they were unable to measure GLS due to image quality or body habitus. GLS was measured in 6 out of 8 control group patients and the sonographer was unable to measure GLS in the other 2 patients due to image quality. The mean global longitudinal strain is significantly reduced in the cobalt study group with -15.2% compared to -18% in the control group (p=0.013 SEM ±0.874) with the difference between the 2 groups is 2.8% (95% CI 0.8 to 4.8) **(Figure 28)**. The Pearson correlation for GLS and blood cobalt in the study population is r 0.74 (p=0.256) and simple linear regression analysis does not demonstrate a significant slope **(Figure 29)**.

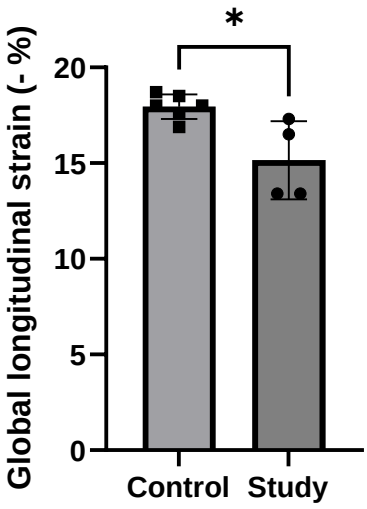


Figure 28: Comparison of Global Longitudinal Strain between patient control and study groups. A histogram showing mean GLS in the study group (n=4) compared to the control group (n=6) (p=0.013) * represents statistical significance p>0.05

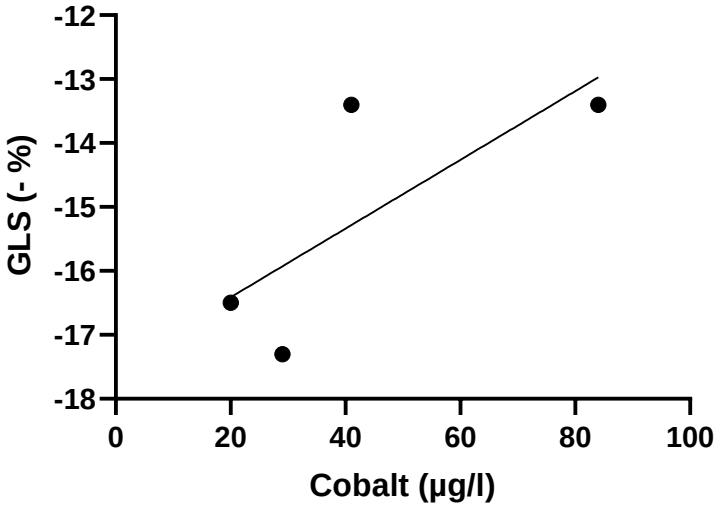


Figure 29: Correlation of GLS with blood cobalt levels in the patient study group. Simple linear regression analysis correlating GLS with blood cobalt levels in the study group**.** (n=4)

However, when a Pearson correlation is performed for every patient who has a GLS result available from both groups it demonstrated a statistically significant correlation of GLS with cobalt level **(Figure 30)**. Pearson correlation of r=0.87 (99% CI 0.5440 to 0.9699, p=0.0009) and simple linear regression demonstrates a significant slope (p=0.0009).

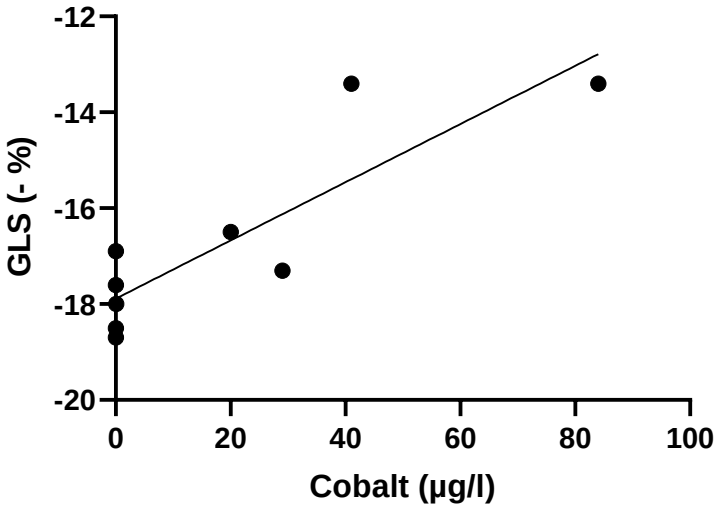


Figure 30: Correlation of GLS with blood cobalt levels in all patients. Simple linear regression analysis correlating GLS with blood cobalt levels in both patient groups. (p=0.0009). (n=10)

LV end diastolic dimension was available for all 12 patients who had under gone echocardiogram in the study group and all 8 in the control group. The mean LV end diastolic dimension is 4.7cm in the study group compared to 5.0cm in the control group (p=0.259, SEM ±0.247) **(Figure 31)** and the difference between the 2 groups is 0.29 (95% CI -0.23 to 0.81). The Pearson correlation for LV end diastolic dimension and blood cobalt in the study population is r 0.13 (p=0.682) and simple linear regression analysis does not demonstrate a significant slope **(Figure 32)**.

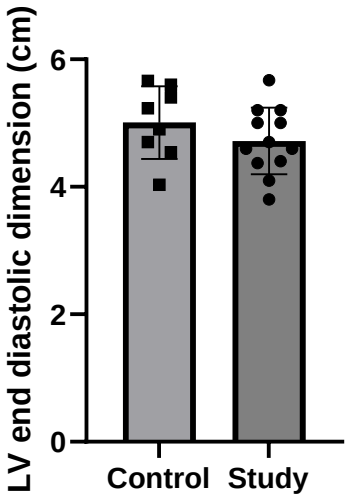


Figure 31: Comparison of LV end diastolic dimension between patient control and study groups. A histogram showing mean LV end diastolic dimension (cm) in the study group (n=12) compared to the control group (n=8) (p=0.259)

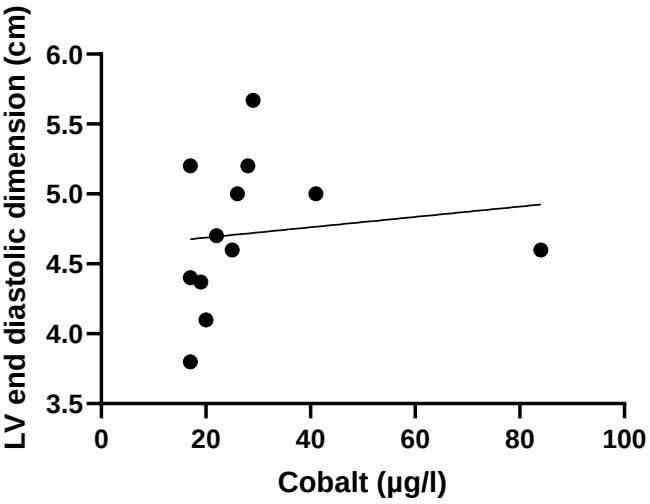


Figure 32: Correlation of LV end diastolic dimension with blood cobalt levels Simple linear regression analysis correlating LV end diastolic dimension with blood cobalt levels. (n=10)

LV wall thickness was available for all 12 patients who had under gone echocardiogram in the study group and all 8 in the control group. The mean wall thickness is 1.2cm in the cobalt study group compared to 1.0cm in the control group (p=0.059, SEM ±0.071) and the difference between the 2 groups is -0.14 (95% CI -0.29 to 0.01) **(Figure 33)**. The Pearson correlation for wall thickness and blood cobalt in the study population is r 0.07 (p=0.824) and simple linear regression analysis does not demonstrate a significant slope **(Figure 34)**.

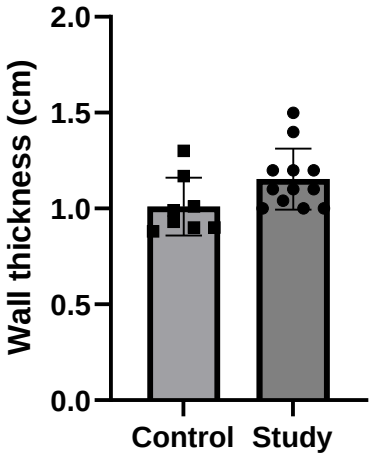


Figure 33: Comparison of wall thickness A histogram showing mean wall thickness (cm) in the study group (n=12) compared to the control group (n=8) (p=0.059)

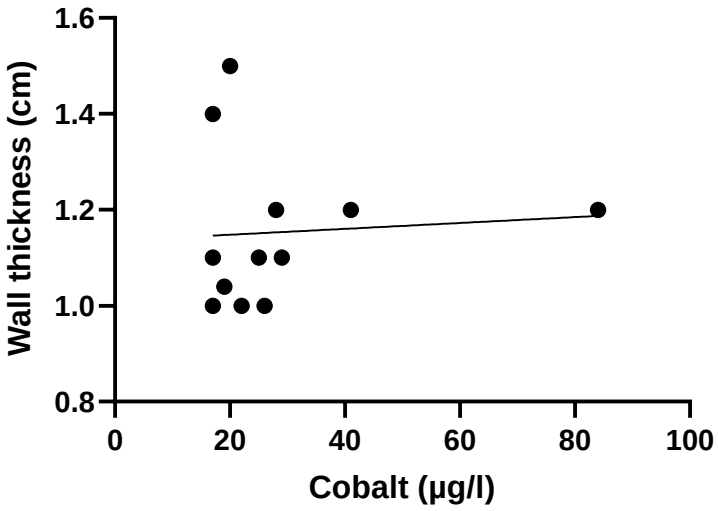


Figure 34: Correlation of wall thickness with blood cobalt levels Simple linear regression analysis comparing wall thickness with blood cobalt levels. (n=10)

	Study Group mean	Control Group mean	Standard error of the mean	Mean P value	Pearson Correlation with blood cobalt	Correlation P value
Age (Years)	70	61	±2.922	0.005	r -0.33	0.217
Heart rate (bpm)	80	78	±7.550	0.717	r -0.41	0.188
Systolic blood pressure (mmHg)	143	152	±7.013	0.165	r -0.41	0.206
Diastolic blood pressure (mmHg)	81	88	±4.819	0.179	r -0.24	0.470
Blood cobalt (µg/l)	29	0.01	±6.348	0.0002		
GLS (%)	-15.2%	-18%	±0.874	0.013	r 0.74	0.256
LVEF (%)	61.5	63.7	±3.688	0.564	r -0.74	0.095
LV end diastolic volume (ml)	103.7	122.7	±16.75	0.279	r 0.12	0.790
LV end systolic dimension (cm)	2.8	3.0	±0.258	0.592	r -0.22	0.492
Fractional shortening (%)	38.9	40.1	±5.041	0.813	r 0.39	0.235
E/e' ratio	8.0	7.8	±0.809	0.771	r -0.22	0.534
LV end diastolic dimension (cm)	4.7	5.0	±0.247	0.259	r 0.13	0.682
Wall thickness (cm	1.2	1.0	±0.071	0.059	r 0.07	0.824

Table 16: Summary of echocardiogram measurements including means, standard error from the means, pearson correlations and p values.

4. Discussion

4.1 Relevance of the study and how it contributes to current literature

This study is the first specifically designed to try and clarify the link between elevated blood cobalt ions and cardiomyopathy in a population of asymptomatic British patients. This study has found that patients with elevated blood cobalt above 13µg/l in the presence of a MoM hip implants have impaired cardiac function, when assessed using GLS, compared to a control group of patients awaiting hip arthroplasty **(Figure 28)**. It has also found a correlation between cobalt levels and GLS **(Figure 30)**. Elevated cobalt at levels over 250µg/l have been shown to be a risk factor for developing systemic complications (Bradberry et al, 2014) and published case reports document cardiac transplantation and death in patients with severely elevated blood cobalt ions (Jenkinson et al, 2021). However, it had previously been unclear whether asymptomatic patients with elevated levels of blood cobalt ions below this threshold were developing cardiac complications. There have been over 1 million MoM hip arthroplasties implanted worldwide (Rising et al, 2012) and population-based studies have shown either a small increase in overall cardiac complications (Lasalle et al, 2018; Gillam et al, 2017) in patients with MoM hips or no difference at all (Goodnough et al, 2018). Previous research has found conflicting evidence as to whether MoM hips cause cardiac complications such as cardiomyopathy(Prentice et al, 2013; Lodge et al, 2018; Berber et al, 2017; Van Lingen et al, 2013; Gillam et al, 2017). This study is the first in the literature to use GLS to assess for any cardiac dysfunction in patients with a MoM hip implant and a normal ejection fraction There has been no previous comparison of patients with elevated blood cobalt levels secondary to MoM hip implants with a population of patients awaiting such implants.

This study increases our understanding of how increased levels of cobalt ions from MoM hip arthroplasties affect the heart. The patient group with MoM hip implants has a mean cobalt levels of 29µg/l and all patients included in the study group have a blood cobalt level above 13µg/l. This study contributes to current knowledge of this problem by assessing a population of British patients who all have blood cobalt levels above 13µg/l. Each patient has undergone a transthoracic echocardiogram which provided a detailed assessment of their cardiac function including, where possible, GLS. GLS is a measure of left ventricular function which can pick up subtle changes in cardiac function which have not yet negatively

affected other echocardiogram parameters (Jung et al, 2020). This study is the first in the literature to use GLS to assess for any cardiac dysfunction in patients with a MoM hip implant and a normal ejection fraction. Previous research published in the literature all chose patients with hip arthroplasties as their control groups. This was either MoM hips with low blood cobalt (Berber et al, 2017) or it was patients with non-MoM hips(Prentice et al, 2013; Lodge et al, 2018 ; Van Lingen et al,2013; Gillam et al, 2017; Lassalle et al, 2018; Goodnough et al, 2018; Sabah et al, 2018; Juneau et al,2019). This study compares a similar group of patients who have no metal implants, although they are awaiting hip arthroplasty surgery, who have a mean blood cobalt of 0.01µg/l **(Table 7)**. This has provided a control group free from confounding factors **(Table 5)** which will allow interpretation of cardiac function to be attributed to circulating levels of cobalt. This is the first such study in the literature.

This study is part of a larger clinical and laboratory project investigating the viability of novel biomarkers for cobalt induced cardiomyopathy. One possible biomarker, Calcium/calmodulin-dependent kinase II delta (CaMKII-delta) is a cardiac protein that is activated early in many forms of heart disease and plays a pivotal role in the pathogenesis of cardiomyopathy (Zhang et al, 2019) (Khoo et al, 2006). CaMKII-delta actively regulates pro-inflammatory signalling pathways contributing to pathologic cardiac remodelling (Rusciano et al, 2019) and animal studies have demonstrated the ability of CaMKII-delta inhibition to restore contraction and relaxation in cardiac muscle (Daniels et al, 2018). Increased CaMKII-delta activity has been observed in pathological cardiac processes which result from dysregulation of Ca^{2+} homeostasis (Wu et al, 2018). This may suggest that CaMKII-delta could be a potentially useful biomarker to detect cardiac dysfunction in patients with elevated circulating blood cobalt levels prior to clinical or echocardiographic changes. Blood samples from patients in both arms of our study are being assessed for a correlation between blood cobalt levels and levels of cardiac proteins including CaMKII-delta. This laboratory arm of the study was delayed due to the Covid. If molecular analyses of the subjects blood demonstrate a link between cobalt levels and altered gene and protein expression then this study will have contributed to our understanding of how circulating cobalt interacts with the heart and will potentially enable clinicians to identify at risk patients who require revision of their MoM implants before they become symptomatic.

4.2 Interpretation of results

This study has demonstrated that patients with elevated cobalt levels above 13µg/l have statistically significant impaired mean GLS compared to a control group of similar patients without hip implants and normal blood cobalt levels **(Figure 28)**. There were no other statistically significant differences in echocardiography measurements **(Tables 12, 13, 14 and 15)**, physiological measurements **(Figures 14, 15 and 16)** or ECG results **(Tables 10 and 11)** between the two groups. When patients from both groups who had GLS performed had their results combined a statistically significant correlation between blood cobalt level and GLS was found and this was confirmed with linear regression analysis **(Figure 30)**. These findings of a decreased GLS with otherwise normal echocardiography in patients with elevated blood cobalt above 13µg/l and a correlation with GLS and blood cobalt levels are new findings which have not previously been described in the literature.

The mean cobalt level in the study group was 29µg/l **(Table 6)**. This group were selected from a group of patients with the highest blood cobalt levels in a regional database and all had ions over of 13µg/l, so a high blood cobalt level was expected. This was statistically significantly higher than the mean blood cobalt (0.01µg/l) of the control group (p=0.0002). The patients in the control group had an undetectable blood cobalt level except for one patient who had 0.1µg/l. 0.1µg/l is in line with the accepted levels for a well-functioning MoM hip implant (Haddad et al, 2011) and so this patient's results being included in the control group should not affect the validity of the results. This is particularly relevant as this is a level of blood cobalt in keeping with the published case reports of cobalt induced cardiomyopathy and patients specifically selected to have this level of blood cobalt have not previously been studied.

The mean age of the study group is 70 years old compared to 61 years old in the control group. The study group were a mean 15 years from surgery when they enrolled in the study **(Table 4)**. In an effort to match the two groups the control group consisted of patients waiting for either a MoM hip resurfacing or a MoP THR. MoM hip resurfacing is performed much more infrequently at present compared to when it was performed on the study group. It is reserved exclusively for younger patients. For the purposes of this study, all members of the study group were over the age of 50. While the mean heart rate was elevated in the study group compared to the control group there was no statistically significant difference between the 2 groups **(Figure 14)**. One of the control group had an

outlying heart rate measured at 128bpm and even when this was removed and the mean of the control group recalculated the increased difference between the two means did not reach significance **(Figure 15)**. Conversely, the blood pressure was slightly higher in the control group, although again, this was not statistically significant **(Figure 16)**. These findings demonstrate that there is no significant physiological difference between a group of patients who have been selected due to having elevated blood cobalt and those with normal levels of blood cobalt. These results demonstrate that the levels of elevated blood cobalt in the study group are not yet having a significant impact on the patients' cardiovascular performance.

Analysis of ECGs for the 2 groups of patients demonstrates that half (50%) of the study group have normal sinus rhythm compared to a majority (62.5%) of the control group **(Tables 10 and 11)**. Of those with abnormal ECGs, 2 patients in the study group had 1st degree heart block compared to none in the control group and 30% of the control group had sinus rhythm with premature ventricular complexes compared to 12.5% of the study group. These abnormal findings are not associated with elevated blood cobalt and do not demonstrate a difference between the 2 groups that can be attributed to elevated blood cobalt (www.nhsinform.scot).

Echocardiography was performed assessing ejection fraction, LV end diastolic volume, LV end systolic dimension, fractional shortening, and E/e' ratio **(Table 12 and 13)** and it was found that these measurements of left ventricular function were not statistically different between the 2 groups. Ejection fraction is the most common measurement for assessing LV function with above 50% being considered normal (Yeboah et al, 2016). Every patient, in both groups, had an ejection fraction above 50% and there was no statistical difference between the two groups **(Figure 19)**. This means that the early cardiovascular changes detected by GLS would have been missed if the patients' were assessed using traditional echocardiography parameters. LV end diastolic volume was 103.7ml in the study group compared to 122.7ml **(Figure 26)** in the control group but this did not reach statistical significance (p=0.2789) despite the control group being just outside the normal range of 62 to 122ml (Clay et al, 2006). The mean end systolic dimension **(Figure 20)** was within normal range for both groups (Harkness et al, 2020) as was the fractional shortening **(Figure 22)** and neither measurement demonstrated a statistically significant difference between the two groups. An E/e' ratio of less than 8 is considered normal and greater than 15 reflects an

increase in the LV filling pressure (Kim et al 2013). The mean E/e' ratio of the study group was 7.8 and for the control group it was 8, with every patient in both groups having a E/e' ratio of less than 11 **(Figure 24)**.

GLS is the only echocardiography parameter which shows a significant difference between the two groups **(Figure 28)** with the study group having an impaired GLS of -15.2% compared to -18% in the control group (p=0.0125). The term "strain" in GLS is used to describe local shortening, thickening and lengthening of the myocardium as a measure of regional LV function (Smiseth et al, 2016). Normal cut off values of GLS are -17% (Asch et al, 2019) although the risk of cardiac disease has been shown to increase on a continuous scale with less risk with a more negative figure (Verdenschot et al, 2021). It has been suggested that while -12% represents severe systolic dysfunction and a significantly adverse prognosis, -15 to -16% represents a risk to patients, such as those in this study, with a relatively preserved ejection fraction (Smiseth et al, 2016). A change from -18% to – 15.2 % is therefore considered a clinically significant change. A study analysing the accuracy of GLS compared to LV ejection fraction in acute heart failure demonstrated that GLS and not LV ejection fraction was an independent predictor of mortality in these patients (Park et al, 2018). In a study of 1296 patients, followed up for 11 years, GLS was shown to predict cardiovascular morbidity and mortality in the general population (Biering-Sorensen et al, 2017). GLS provided incremental prognostic information with men with a GLS greater than -15.8% having a 5 times greater risk of developing heart failure over an 11 year period than men with a GLS of less than -18%. Overall, patients with worsening GLS had increasing rates of heart failure, myocardial infarction and cardiovascular death. (Biering-Sorensen et al, 2017). Hypotension, dilated cardiomyopathy and reduced contractility have been previously associated with cobalt, and while the patients in this study have not developed these signs, the previous studies suggest that if followed up for long enough these signs will become evident (Smiseth et al, 2016, Park et al, 2018, Biering-Sorensen et al, 2017).

The values for LV end diastolic dimension **(Figure 31)** and LV wall thickness **(Figure 33)** were not statistically significantly different between the two groups and were within normal ranges with the mean LV wall thickness in the study group being at the upper end of normal (Harkness et al, 2020). Overall the number of patients described as having left ventricular hypertrophy was not statistically different, 3 out of 12 in the study group **(Table 14)** and 1 out of 8 in the control group **(Table 15)** in keeping with the individual measurements.

Heart failure with normal ejection fraction, sometimes also known as heart failure with preserved ejection fraction (HFpEF) (Zile et al, 2001), is a condition where patients presenting with the symptoms of heart failure have a normal ejection fraction and is often under diagnosed leading to deteriorating cardiac function (Sanderson, 2007). GLS has been shown to be more sensitive than ejection fraction at picking up cardiac damage in early cardiomyopathies (Verdonschot et al, 2021), Chronic Kidney Disease (CKD) (Krishnasamy et al, 2015) and heart failure (Cho et al, 2009). The mean GLS in the group with elevated cobalt in this study had a mean blood cobalt worse than the World Alliance Societies of Echocardiography Normal Values Study lower limit of normal GLS of -17% in men (Asch et al, 2019) at -15.2% while the control group had a GLS which was within normal values. This level of GLS is similar to that demonstrated in Copenhagen to have a 2 times higher risk of cardiovascular death over an 11 year period than patients with similar levels of GLS as our control group (Biering-Sorensen et al, 2017). The current study has demonstrated that the group of patients with blood cobalt levels above 13µg/l have impaired GLS compared to the population with normal blood cobalt levels despite there being no difference in other echocardiography parameters between the two groups. Ejection fraction was normal for every patient in both groups. This would suggest that the patients with impaired GLS are developing early cardiac damage which may progress to heart failure, myocardial infarction and cardiovascular death.

4.3 Comparison to previous research

This study demonstrates that asymptomatic patients with elevated blood cobalt ions, below the level linked with severe cardiac complications, are demonstrating early cardiac damage. The blood cobalt levels in this study are higher than those described by Prentice et al (2013) who found evidence of cardiac changes in MoM patients and similar to the studies by Lodge et al (2018) and Berber et al (2017) which did not demonstrate any cardiac dysfunction. These 3 studies all had control groups whose patients had had a hip arthroplasty. Prentice and Lodge both chose patients with non-MoM hip arthroplasties while Berber chose a mix of MoM patients with low blood cobalt and CoC patients. The control group inclusion criteria in the cited studies differ from the choice of patients in this study as it was decided to include patients awaiting hip arthroplasty without any metal in situ. The reasons for this choice were varied; primarily it was due to the risk of trunnion wear at the head/neck junction in all hip arthroplasty patients leading to release of metal ions (Mistry et al, 2016).

While the risks of metal ion release from trunnions may be at lower levels than in MoM hips, it was felt that in order to give as clear a difference between the two groups as possible then the control group in this study should have no metal implants and therefore no risk of arthroprosthetic cobalt release. Prentice et al (2013) analysed asymptomatic patients and found a difference in echocardiogram measurements with even low levels of blood cobalt ions. They described a difference in ejection fraction and LV end diastolic diameter which was impaired in their population of patients with a mean blood cobalt of 1.75µg/l which was not reproduced in this study of patients with higher blood cobalt levels. Lodge et al (2018) demonstrated increased heart volume on echocardiogram but no clinically relevant changes in a population with blood cobalt levels of 14.6µg/l and Berber et al (2017) found no relationship between blood cobalt levels and ejection fraction. Van Lingen et al (2013) found no signs or symptoms of cardiomyopathy in 10 patients with mean blood cobalt levels of 46.8 µg/l. None of these previous studies made use of GLS which has been shown to detect cardiac conditions in patients with normal ejection fraction. The findings in this study of impaired cardiac function as assessed by GLS **(Figure 28)** add to the previous research in demonstrating that elevated blood cobalt levels below 250µg/l (20µg/l to 84µg/l) can still lead to impaired cardiac function and possibly cardiomyopathy. Gillam et al (2017) found that men with an ASR XL THA had a statistically significant higher rate of hospitalization for heart failure than men with a MoP THA. Gillam studied a specific implant, the ASR XL hip arthroplasty. These findings add to the overall knowledge and are transferrable to the general MoM patient population. The population of patients who have historically undergone MoM hip arthroplasty have received a very heterogenous group of implants with wildly differing surgical outcomes and revision rates (Rising et al, 2012) and this present study has sought to reflect this by including patients with a variety of implants. This should provide more transferable results to all MoM patients with elevated blood cobalt levels.

Due to the large numbers of MoM hip arthroplasties performed, recent clinical studies have tried to determine the risk of cobalt cardiomyopathy posed across entire populations of patients. However, population-based studies are designed to demonstrate epidemiological trends and do not specifically address the risks of cardiomyopathy in patients with elevated blood cobalt ions. A number of implant population studies did not analyse or report blood cobalt levels for the patients they studied. A consequence of excluding such a key variable in studies can result in contradictory findings being reported which are difficult to relate to

individual patients potentially at risk of cobalt-induced cardiomyopathy due to their elevated blood cobalt. For example Lasalle et al (2018) identified a small increase in heart complications in French patients with metal bearing surfaces compared to non-metal surfaces after controlling for confounding factors which was most pronounced in MoM v CoC in women and men over 75 years of age. Yet an analysis of the Standards Analytics Files database in the United States comparing every patient who had undergone a MoM hip arthroplasty between 2005 and 2012 to an age and sex matched cohort who had undergone a non-MoM hip arthroplasty in the same period found at 5 years there was no difference in cardiac complications such as cardiac failure, arrhythmia, acute myocardial infarction or cardiomyopathy (Goodnough et al, 2018). Additionally, a retrospective analysis of over half a million hip arthroplasty patients in the United Kingdom's National Joint Registry including 53,529 MoM patients demonstrated no association between a MoM implant and cardiac failure at 7 years post operatively. These studies demonstrate the overall safety of MoM arthroplasty when performed well in appropriate patients, however, they do not provide an answer as to whether or not MoM implant patients with elevated blood cobalt levels are at risk of cobalt-induced cardiomyopathy.

4.4 How it will affect clinical practice

This study has demonstrated that patients with blood cobalt levels above 13µg/l can have impaired cardiac function as assessed by GLS even with a normal ejection fraction. While the blood cobalt levels reported in this study are elevated they are not as high as most of the patients with cobalt-induced-cardiomyopathy identified in the case reports (Jenkinson et al, 2021). The mean blood cobalt in this study is 29µg/l compared to 326µg/l in the case reports. This demonstrates that cardiac damage is occurring at lower blood cobalt levels than previously reported. The MHRA cut off, above which patients with MoM hips require further investigation is 7µg/l. These investigations should now include echocardiogram, including GLS. Taking this study's finding into consideration, future clinical guidance may wish to consider that all patients with blood cobalt levels above 13µg/l should be assessed for cardiac changes with an echocardiogram and, where possible, this should include GLS. Currently revision of MoM implants occurs if the patient is symptomatic or significant soft tissue destruction is found on imaging (MHRA, 2017). In patients where evidence of cardiac damage may be linked to elevated blood cobalt, then revision of MoM implants in patients with otherwise asymptomatic hips may be considered. At this stage in our understanding of

the condition cardiac function should be one of the factors taken into account rather than the determining factor but with further research on the subject this could become a more important part of our treatment algorithm. Selected patients are still receiving MoM implants and they should have a more detailed cardiac work up prior to surgery in order to detect any underlying cardiac condition which could be exacerbated by a poorly functioning MoM hip implant causing severely elevated blood cobalt levels.

4.5 Strengths, limitations of study and how it could be improved

4.5.1 Strengths

This study is the first to use GLS to assess for evidence of cardiac dysfunction in patients with elevated blood cobalt. GLS has been shown to be more sensitive at picking up cardiac damage in early cardiomyopathies (Verdonschot et al, 2021) than standard echocardiography measurements such as ejection fraction. This allows us to demonstrate a significant difference between the two populations which would not have been apparent had the echocardiograms been limited to ejection fraction.

The West of Scotland MoM database covers a population of over 2.5 million people and even with a robust exclusion criteria this allowed sufficient patient numbers to facilitate recruitment of 20 patients with a documented blood cobalt level over 13µg/l. This study has demonstrated impaired cardiac function in asymptomatic patients with elevated blood cobalt lower than the exceptionally high levels associated with clinical cardiomyopathy in the case reports (Jenkinson et al, 2021). The range of blood cobalt levels included in the study group (17 to 84µg/l) make this study clinically relevant to surgeons with a MoM arthroplasty practice and may influence future guidelines.

4.5.2 Effects of Covid-19 Pandemic

The coronavirus pandemic has unfortunately affected this study in numerous ways. Primarily it caused significant delays to the recruitment of patients. Recruitment clinics were initially scheduled for the end of March and beginning of April 2020. Due to the first wave of the virus these clinics were cancelled and the study postponed by 6 months. The clinics eventually took place in October 2020 and April 2021. The length of time between clinics was due to further lock downs. It was straightforward to justify reviewing the study group as patients with severely elevated blood cobalt require annual follow up of their MoM hip and this review was combined with enrollment into the study. Asking the control

group to attend hospital during a pandemic when they would not have been there otherwise was ethically more problematic, therefore the first 3 patients in the control group were recruited in April and the remaining patients recruited in early August 2021.

The COVID pandemic has had a negative effect on both the length of time it has taken for echocardiograms to be performed and also more disappointingly in the standardisation of echocardiogram assessments. After discussion with Professor Brady, an academic cardiologist in Glasgow Royal Infirmary, and Denise Skedd, the senior sonographer it was agreed that all patients would undergo an echocardiogram performed by a single radiographer, using a standardised protocol, which included GLS. Unfortunately, due to problems accessing the service caused by the pandemic this did not happen. Patients underwent echocardiography in different hospitals closer to their home and 4 patients who were enrolled in the study were still awaiting echocardiograms at the time of submission of this thesis. Sonographers in peripheral hospitals did not perform echocardiography using the agreed protocol and this led to not all patients having GLS measured.

4.5.3 Limitations of study

The limitations caused by the covid pandemic, particularly the lack of standardization of echocardiograms caused by more than 1 sonographer taking part, may have affected the outcome of the study. Only 4 patients in the study group and 8 in the control group had GLS performed. This was partially due to the pandemic and partially due to the *body habitus* of some patients. This may affect the validity of the results, however, as the difference between GLS in the 2 populations was statistically significant even with smaller numbers there is confidence that this study's findings are still clinically relevant.

Ethical approval was granted for 30 patients to be enrolled in the study. It was decided to include 20 patients in the study group and 10 in the control group in order to increase the chance of finding cardiac abnormalities in a patient with elevated cobalt. Patients withdrew from the study or were unable to travel to Glasgow for their echocardiograms leaving at this time 12 patients who underwent echocardiograms in the study group and 8 in the control group. As the sonography service catches up with the post-covid backlog it is planned that more of the two groups will undergo echocardiograms with GLS.

The control group were selected from the waiting list for hip arthroplasty and the same general inclusion and exclusion criteria as the study group were applied. While the patient

demographics were broadly similar (mean age 70 in the study group compared to 61 years of age in the control group), more care could have been taken to match the patients identically for age and comorbidities. However, as both groups did not have significant cardiac, neurological or endocrine comorbidities when they were enrolled in the study they were considered a close enough match.

The initial identification of patients took place in September 2019 and echocardiograms were still being performed in June 2022 due to pressures on the sonography service brought about by the pandemic. A study lasting 33 months in an elderly population has meant that some patients' medical condition has changed. At enrollment, all patients had no history of cardiac conditions. Over the course of the study 1 patient in the study group developed atrial fibrillation and 1 developed hypertension. Two patients in the control group developed hypertension. All were well controlled with appropriate medication. These patients were kept in the study and their echocardiography results analysed as overall cardiac health could be related to the presence or absence of elevated cobalt. Sadly one patient in the study group passed away during the study, from non-cardiac conditions, although he had already undergone his echocardiogram.

4.5.4 Improvements to the study

This study could be improved by addressing some of the limitations discussed above. Larger numbers of patients recruited into both groups would make it more likely to pick up statistically significant differences in other echocardiography measurements apart from GLS. In order to find more than twenty patients with blood cobalt above 13µg/l the sample population could be expanded from the West of Scotland to the whole of Scotland, the entire United Kingdom or further afield. A larger study enrolling patients from multiple centres would provide a larger sample size to increase the significance of the results. This study could also have been improved by ensuring that all patients underwent their echocardiogram by the same sonographer and that all patients had GLS measured.

4.6 Ongoing and future research

Further study in this field would enroll all patients with elevated blood cobalt above the MHRA recommended 7µg/l secondary to MoM hip implants and arranging for them to undergo an echocardiogram including GLS. Echocardiograms for this expanded population group would be analysed to determine if there is a cut off value for blood cobalt above

which patients are at risk of developing cardiomyopathy. Patients undergoing revision hip surgery to remove MoM implants and replace them with other forms of hip arthroplasty could be assessed both before and after revision surgery with an echocardiogram including GLS.

This study is part of a larger clinical and laboratory project looking at the viability of novel biomarkers for cobalt induced cardiomyopathy. Future research could include analyzing cardiac biomarkers along with the echocardiograms to assess cardiac health in this population of patients. Cardiac biomarkers could be investigated to determine if they can provide an earlier indication of cobalt induced cardiomyopathy. One possible biomarker, Calcium/calmodulin- dependent kinase II delta (CaMKII-delta) is a cardiac protein that is activated early in many forms of heart disease and plays a pivotal role in the pathogenesis of cardiomyopathy (Zhang et al, 2019) (Khoo et al, 2006). CaMKII-delta actively regulates pro-inflammatory signaling pathways contributing to pathologic cardiac remodeling (Rusciano et al, 2019) and animal studies have demonstrated its inhibition restores contraction and relaxation in cardiac muscle (Daniels et al, 2018). Increased CaMKII-delta activity has been observed in pathological cardiac processes which result from dysregulation of Ca 2+ homeostasis (Wu et al, 2018). This may suggest that CaMKII-delta could be a potentially useful biomarker to detect cardiac dysfunction in patients with elevated circulating cobalt levels prior to clinical or echocardiographic changes. Blood samples from patients in both arms of our study are currently being assessed for a correlation between blood cobalt levels and cardiac proteins expression levels including CaMKII-delta.

4.7 Conclusion

This study has demonstrated reduced cardiac function, as assessed by GLS, in patients with elevated cobalt above 13µg/l secondary to MoM hip implants despite the presence of a normal ejection fraction and other echocardiography parameters. These patients have a statistically significantly impaired GLS compared to a control group of patients with normal blood cobalt. As GLS is a more sensitive measure of systolic function than ejection fraction, routine echocardiogram assessment including GLS should be performed in all patients with MoM hip arthroplasties and elevated blood cobalt above 13µg/l. Further work is recommended to assess if these cardiac changes are present in patients with elevated

blood cobalt levels above the MHRA cut off level of 7µg/l and if they will improve following revision surgery.

This study supports the hypothesis that patients with elevated blood cobalt above 13µg/l in the presence of a MoM hip implant have impaired cardiac function compared to a control group of patients awaiting hip arthroplasty.

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