Ventricular-Arterial Coupling in Maternal Heart Disease and Its Association with Fetal and Uteroplacental Outcomes in the Mid-trimester of Pregnancy

by

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Abstract

Background: Maternal heart disease (MHD) or heart disease during pregnancy, which can be congenital (CHD) or acquired (AHD), affects 4% of all pregnancies and is associated with increased maternal and fetal complications. Some have proposed cardiac dysfunction to be responsible for these complications. However, not all MHD pregnancies with maternal or fetal complications have significant cardiac dysfunction suggesting that other factors could be contributory. Vascular health has been seen to be affected in non-pregnant populations with CHD and complicated pregnancies without MHD. Therefore, we chose to examine ventricular-arterial coupling (VAC), a measure of cardiovascular function which incorporates both vascular load and left ventricular (LV) efficiency/function in MHD and control participants. An increase in VAC will either suggest increased arterial load, decreased LV efficiency or a combination. Therefore, as we chose to focus on cardiac health, we hypothesized that VAC would be increased in MHD, at least partly due to reduced LV efficiency or function. We also hypothesized that increased VAC would be associated with poor uteroplacental and fetal health in the midtrimester of pregnancy.

Methods: Participants with and without MHD were recruited between 18-24 weeks of gestation (midtrimester) to undergo transthoracic and fetal echocardiography. Groups were matched by maternal age, pre-pregnancy body mass index and body surface area. Metrics of cardiovascular function including VAC, cardiac output (CO), LV ejection fraction (LVEF), global longitudinal strain and E/E' were obtained by thoracic echocardiography. VAC was calculated as arterial elastance (Ea)/end-systolic elastance (Ees) using LV volumes and LVEF, blood pressure and the preejection/total systolic period. Fetal biometry and Doppler-based uterine (UtA) and umbilical (UA) artery pulsatility indices (PI) were assessed by fetal echocardiography with comparisons

made in centiles. Depending on the normality of the distribution of a given outcome, independent samples t-test or a Mann-Whitney U statistical test were used to compare outcomes between MHD and control participants. One-way ANOVA or a Kruskal-Wallis test for nonparametric data were used to compare outcomes between severity of MHD (mild or moderate-severe) and controls.

Results: We recruited 33 MHD (29 CHD , 4 AHD, mean 20.0±1.2 weeks gestation) and 32 control (21.5±1.6 weeks) pregnancies. Maternal heart rate and blood pressures did not differ among groups. VAC was higher in MHD compared to controls (0.78±0.15 vs 0.69±0.01, P=0.0063), with highest values in those with moderate-severe MHD (0.80±0.18 vs controls, P=0.009), suggesting reduced cardiac function or increased arterial load in MHD. Reduced cardiac function was supported by a lower Ees in MHD, reflecting reduced LV efficiency/function. Although CO, global longitudinal strain and strain rate did not differ, other measures of cardiac function were affected in MHD including LVEF and E/E'. LVEF was significantly reduced in MHD vs controls (61±9% vs 67±6%, P=0.0033) and E/E' higher (median [IQR]: 7.1 [3.7] vs 5.8 [1.9], P=0.015), especially in those with moderate-severe MHD. Finally, UtA-PI, UA PI and fetal biometry were similar among groups , however, 10% of MHD vs 0% of controls had a UtA-PI >95th centile.

Conclusion: Increased VAC in MHD could suggest the presence of reduced LV function, increased arterial load or both in affected pregnancies. Reduced absolute Ees, and LVEF and increased E/E' indicate reduced cardiac function in MHD, possibly contributing to increased VAC. Uteroplacental and fetal health are preserved at this point in pregnancy despite increased VAC in MHD.

Preface

This thesis is an original work by Juliana Lasso Mendez. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “The Role of Vascular Dysfunction in Pregnancies Complicated by Maternal Heart Disease and its Contribution to Adverse Pregnancy Outcomes”, Pro00084169_AME7, July 27, 2020.

Dedication

To my parents, whose unwavering love and selflessness have provided me with a life full of possibilities.

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CHAPTER 1: INTRODUCTION

Introduction

Maternal heart disease (MHD), which includes congenital (CHD) and acquired (AHD) subtypes, affects 4% of all pregnancies and is the leading cause of maternal mortality [7, 8]. MHD is on the rise, at least in part due to improvements in the medical and surgical care of infants, children and adolescents with CHD leading to increased survival [9]. Surveillance data from Quebec, for instance, demonstrated that the mortality of youth (<20 years of age) with CHD decreased from 49% to 9% between 1987-1988 to 2004-2005, respectively [10]. As a result of this trend, the number of adults with complex CHD now outnumber the affected children [11] resulting in an increasing number of people with CHD surviving to and through reproductive age. In addition, more women are also becoming pregnant later in life (>35 years of age) [12], which is increasing the risk for the development of AHD prior to and during pregnancy, and further contributing to a rise in the incidence of MHD [8].

From a multicenter study in Canadian hospitals, it was estimated that among MHD pregnancies 74% have CHD and 22% AHD [13]. Although most individuals suffering from known CHD or AHD are able to become pregnant, these pregnancies carry higher rates of complications compared to healthy pregnancies including cardiac (2-13%), obstetrical (2-19%), and fetal/neonatal (2-25%) complications depending on how they affect the mother and/or offspring [13-17]. Although AHD is less common than CHD in pregnancy, it carries a higher risk of complications than CHD [7, 18]. In fact, the complications observed in MHD vary with the pathophysiology and severity of the CHD or AHD [14]. The latter of which is established depending on the degree to which cardiac structure and hemodynamics are altered [19-22], where more significant alterations of normal heart physiology will potentially promote a higher occurrence of

complications. With the current trends, as more individuals present with MHD in pregnancy and encounter complications, it becomes increasingly important to understand underlying mechanisms contributing to poor maternal, fetal, and neonatal outcomes in this population to predict risk of complications and to develop potential treatment strategies.

The mechanisms underpinning adverse pregnancy outcomes in MHD are poorly understood. However, given the nature and sequalae of the underlying disease, cardiovascular health is likely a major factor [23]. Both the heart and vascular system play essential roles in maintaining a successful pregnancy and in supporting the necessary adaptations to ensure an adequate supply of nutrients and oxygen to the developing fetus [6, 24]. Myocardial dysfunction can be present in repaired CHD, and there is also evidence for altered vascular health in affected adults and children, but whether they contribute to complications associated with MHD has not been well studied. Vascular dysfunction, however, has been linked to complications in pregnancies without MHD [25-29]. An assessment of the interaction of the heart and vascular system could provide insight into the pathophysiology of MHD pregnancies and its possible contribution to cardiac, obstetrical and fetal/neonatal risks observed in these populations.

Ventricular-arterial coupling (VAC), a measure of cardiovascular performance that incorporates arterial load (Ea) and left ventricular (LV) efficiency or function (Ees), may be altered in the setting of altered myocardial or vascular health or a combination thereof [30-32]. To date, there is a paucity of data on VAC in pregnancy in general and only one study has evaluated VAC in a milder spectrum of MHD [33]. Therefore, it is unknown how altered VAC due to either reduced LV function, increased arterial load or both might be related to complications or the risk of complications in MHD. Current risk assessment for complications in MHD is limited. It is primarily done with the general cardiac symptom-based New York Heart Association (NYHA)

Functional Classification for risk of heart failure, as well as two pregnancy-specific risk classifications, the modified World Health Organization (mWHO) and Cardiac Disease in Pregnancy (CARPREG) 1 and 2 classification systems [13, 19-21, 34, 35]. mWHO was generated based on known maternal risks for morbidity and mortality, whereas, the CARPREG classification systems are focused on maternal risk for cardiac complications. However, none of these incorporate the interaction between myocardial and vascular function (VAC) and the individual contributions of both components to risk of poor outcomes, and neither include fetal/neonatal mortality and morbidity risks. Further investigation into the underlying cardiovascular mechanisms in MHD that could be mediating the adverse outcomes, including the contribution of altered VAC, would perhaps allow for better risk stratification. This could also enable specific targeting of cardiac or vascular parameters for treatment to prevent or mitigate adverse outcomes in these pregnancies.

The following review will begin with an exploration of the various cardiovascular adaptations that must take place during a normal pregnancy. Elaboration of the different maternal, neonatal, and fetal complications associated with MHD will be provided, including a summary of cardiac mechanisms believed to be mediating these complications based on the existing literature. The current clinical approach to pregnancy risk stratification in MHD will be presented in greater detail. Finally, the potential contribution of altered vascular health with consequent changes in ventricular-arterial coupling in MHD will be explored, all of which have prompted the current research.

Cardiovascular Adaptations in Normal Pregnancy

Over 40 weeks, the time for full-term gestation, significant maternal cardiovascular adaptations must occur to ensure adequate supply of nutrients and oxygen to the fetus [36] (Figure 1-1). To support the growing fetus, the maternal heart must increase the amount of blood it pumps every minute, also referred to as the cardiac output (CO) [1, 37]. The rise in CO begins as early as 5 weeks of gestation, continues to increase throughout the first and second trimesters, reaches a plateau in the second trimester and remains elevated compared to baseline pre-pregnancy measures through the end of pregnancy [4, 6, 38]. It is generally accepted that by the end of a healthy term pregnancy, the maternal CO increases by 30-45% over preconception levels [39-41], and has been observed to return to preconception values usually by 16 weeks postpartum [3].

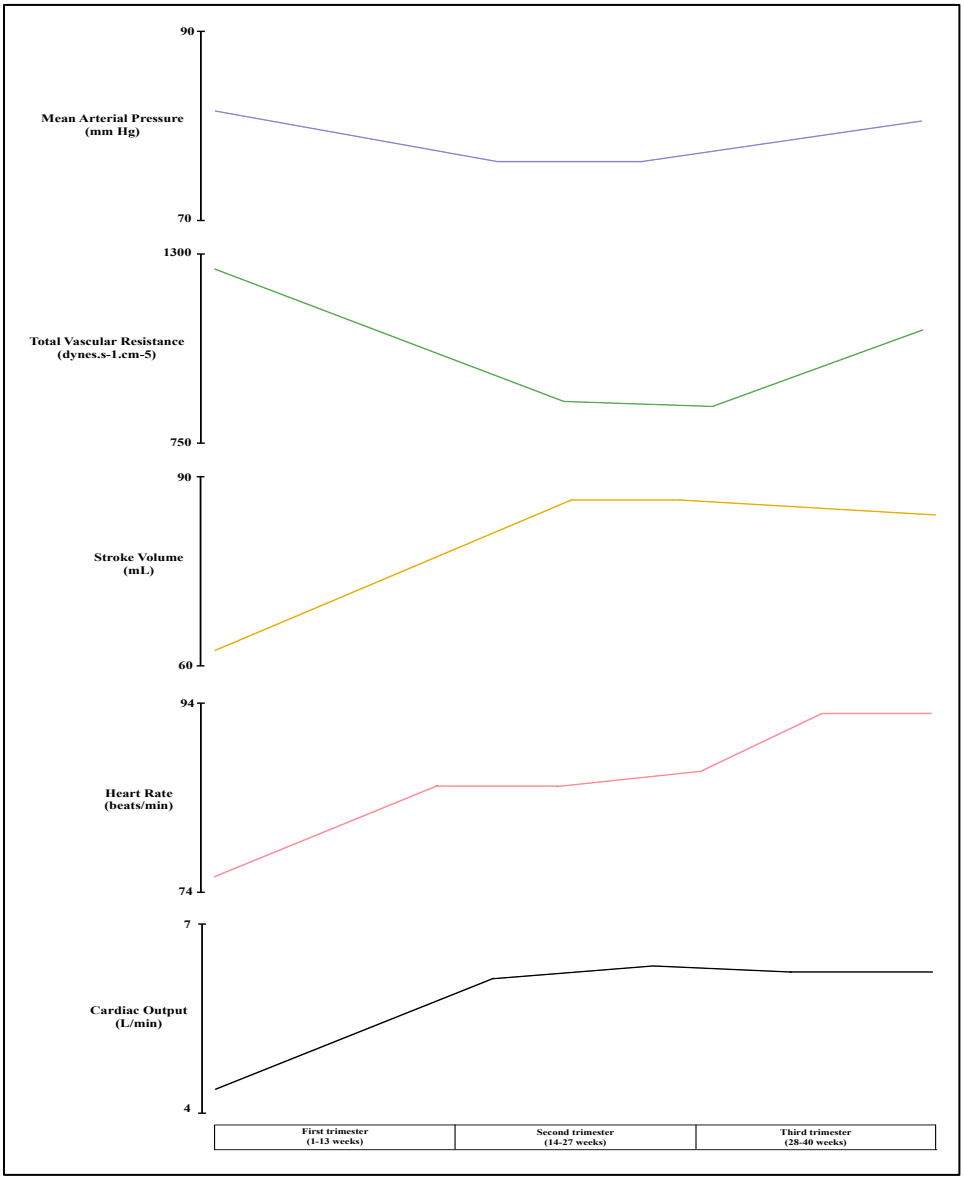
CO is the product of stroke volume and heart rate and will therefore increase as a result of changes of one or both of these two parameters [42] . Stroke volume, which has been shown to be proportional to alterations in body surface area (BSA), starts increasing by the 5th week of pregnancy in a linear-like manner reaching a maximal volume during the second trimester (~30% increase over preconception values) [40, 41, 43]. In the third trimester, stroke volume begins a gradual decline towards pre-pregnancy values perhaps due to a concomitant increase in blood pressure in the same period of gestation [2, 3, 6]. Whether the normal maternal myocardium has also reached its diastolic capacity to sufficiently preload, as well, is not known. Maintenance of a high CO in the third trimester is mediated by an increase in heart rate [6]. The increase in heart rate begins during the first trimester and reaches a peak in the third trimester which is at 20-25% over preconception values [2, 40, 41, 43].

The left ventricle (LV) in the normal heart supports the systemic circulation, and in pregnancy, this includes providing blood to the uterus. In the in series human circulation, the right

ventricle must also provide a comparable output to the lungs, both to oxygenate the blood and sufficiently preload the LV to do its work ejecting to the body. Given the importance of the LV in supporting the systemic and uterine circulation, and its interface with the systemic vascular system, the remainder of this section will focus on the contribution of maternal LV health in pregnancy.

In order for the CO and LV stroke volume to increase during pregnancy, multiple aspects of the cardiac physiology must adapt and some must remain intact including LV contractility [42]. Contractility is an intrinsic characteristic of the ventricle that is not affected by the force the ventricle must work against to eject blood (i.e. afterload), and minimally affected by the force that stretches and loads the myocardium prior to the systolic contraction (i.e. preload) [44-46]. LV contractility is clinically evaluated by assessing myocardial strain through speckle tracking echocardiography, a method believed to be more reliable at reflecting contractility due to its lower load-dependency (i.e. affected by preload and afterload) [47, 48]. Myocardial strain, commonly known as global longitudinal strain, is quantified as the percentage deformation of the muscle fibers compared to the fibers' original length, typically expressed as a negative value [49]. Both Cong et al [50] and Sengupta et al[51] demonstrated a decrease in maternal LV global longitudinal strain throughout pregnancy with the greatest decrease in the third trimester compared to baseline values from non-pregnant subjects (~13% decrease in both cases). The values returned to baseline in the postpartum period. This suggests that in normal pregnancy, LV contractility may be reduced in the third trimester. Some argue that these changes might be due to a slight hypertrophy of the LV due to increased circulating blood volume, which is normally reversed in the postpartum period [50, 52] , as it has been shown that myocardial deformation changes with altered LV geometry (i.e. hypertrophy and increased sphericity in pregnancy) [51, 53] .

Figure 1-1: Summary of Various Cardiovascular Adaptations in Normal Pregnancy



Values and trends obtained from Hall et al [1], Hunter et al [2], Mahendru et al [3], Melchiorre et al [4], Moutquin et al [5] and Sanghavi et al [6].

Other aspects of cardiac function such as the LV ejection fraction (LVEF) remain intact to maintain an optimal CO [42, 54]. LVEF, the proportion of blood ejected by the LV following its filling, is highly load-dependent, reduced with increased afterload and normally increased with higher preload, and will increase with greater contractility [45]. LVEF appears to be preserved throughout pregnancy, at least partly through a decrease in afterload [4] and increased preload [51], despite the finding suggestive of reduced myocardial contractility [40, 55, 56].

In normal pregnancy, preload, the stretch of the myocardium in end diastole [45], has been shown to increase linearly as a consequence of increasing filling volumes [57]. Afterload decreases in pregnancy and this is achieved in part by decreasing vascular resistance (~20-45% from preconception) [3, 4, 6, 43, 58] and mean arterial pressure, at least until the early 3rd trimester, as well as an increase in arterial compliance [1, 4, 36]. Vascular resistance will decrease from preconception values and appears to be lowest in the second trimester. It will thereafter plateau or have a subtle increase throughout the third trimester [3, 4, 6, 58]. Given that vascular resistance is the force that vessels exert on blood [59], its decrease would result in decreased afterload on the heart potentially allowing for an increase in SV and subsequently CO [46]. Concomitant with changes in systemic vascular resistance, mean arterial pressure has been shown to decrease beginning with the first trimester, reaching a nadir between 16-20 weeks. Thereafter mean arterial pressure increases throughout the second and third trimester reaching values at the end of pregnancy similar to those at preconception [1, 3-5]. Arterial compliance is thought to increase throughout pregnancy at least partly due to relaxin, a peptide hormone primarily produced in the endometrium [1, 60-62]. It appears that relaxin promotes vascular remodeling resulting in more compliant vessels [63]. Arterial compliance will start with an increase from baseline values to the first trimester. It will plateau from the first to second trimester, but will have a drastic increase through the second to third

trimesters contributing to decreased afterload [58]. Compliance refers to the ability of the vessels to expand and increase volume for a given pressure [64]. Given its increase during pregnancy, this allows for the accommodation of increased volumes in the vessels resulting from an increased CO [58, 65].

As seen throughout this section, the synchronized adaptation of various cardiovascular parameters ensures delivery of nutrients and oxygen to the fetus ultimately through an augmented CO. Whether the demands of pregnancy, which require important cardiac and vascular adaptations, can be accommodated in the context of MHD is currently not fully known, however, the increased risks of obstetrical and fetal/neonatal complications suggest a role for inadequate cardiovascular adaptations.

Heart Disease and Pregnancy

The adaptations observed in a healthy uncomplicated pregnancy represent a significant stress to the cardiovascular system that may further challenge those with MHD. This is particularly true if there are cardiac structural alterations or dysfunction at baseline [66]. This might contribute to various cardiac complications including arrhythmias and heart failure, and obstetrical complications such as hypertensive disorders, preeclampsia, peripartum cardiomyopathy, and postpartum hemorrhage (perhaps due to use of anticoagulant medication and mode of delivery) [7, 13, 16, 20, 66, 67]. Thus, knowledge of the underlying pathophysiology that culminates in these adverse outcomes is critical to improving the health of these pregnancies.

Types of MHD

MHD in pregnancy can either be congenital or acquired with CHD representing nearly three-quarters of cases.[13] CHD includes a broad spectrum of congenital malformations of the heart, ranging from those that are life-threatening and require surgical intervention early in life, to milder disease that can self-resolve or, even following repair, has no impact life-long [20]. Some of the most severe and complex forms of CHD which have been linked to increased risk of maternal morbidity and mortality include a functional single ventricle most status-post a Fontan procedure, transposition of the great arteries, particularly those post atrial switch procedures, severe left heart obstruction including mitral and/or aortic stenosis and coarctation of the aorta [19-21, 68]. With respect to AHD, previous peripartum cardiomyopathy with impaired LV function has been associated with high maternal mortality and severe morbidity risk [19-21, 68]. Rheumatic heart disease resulting in mitral stenosis, has also been associated with increased morbidity as a result of the occurrence of heart failure and arrhythmias [66, 69].

Congenital Heart Disease: Milder categories of CHD that normally have a low maternal risk for mortality and morbidity, especially if repaired, include left to right shunts and mild pulmonary stenosis[19-21, 68]. More severe forms can include left and right heart obstruction depending on the degree of obstruction and cyanotic MHD (i.e. transposition of the great arteries, tetralogy of Fallot, functional single ventricle) [20, 23]. Left to right shunts, as the name depicts, are lesions in which oxygenated blood flows from the left to the right side of the heart. These include atrial and ventricular septal defects and patent ductus arteriosus [70]. Most individuals with these lesions support pregnancy without complications [71]. However, they become problematic when the LV

(ventricular septal defect or ductus arteriosus) or right ventricle (atrial septal defect) must eject a larger output to the lungs whilst maintaining adequate flow to the body. When large, shunts also contribute to increased pulmonary pressures, all of which can be a challenge in pregnancy if unrepaired [66]. If pressures were to increase significantly, thus increasing the afterload for the right heart and there is heart function, given the need for pulmonary venous return to the left heart, the CO would eventually be reduced [72]. One could argue that this could potentially lead to organ underperfusion, including the uterus, resulting in reduced uteroplacental flow, and affecting fetal health [73].

Obstructive lesions represent a large spectrum of CHD and can be accompanied by a high risk of maternal mortality if severe [19-21]. Left heart obstructive lesions include pathologies such as aortic valve, subvalve or supravalve stenosis, coarctation of the aorta, bicuspid aortic valve and mitral valve stenosis [74]. In the case of severe obstruction, the LV might be limited in its capacity to increase its CO. Furthermore, increased systolic and diastolic filling pressures particularly, most observed in LV outflow tract obstruction, could impact the ability of the LV to augment its preload and promote the evolution of clinical heart failure due to high LV filling pressures [66]. In mild aortic stenosis, maternal mortality is low [75], however, obstetrical complications have been observed in individuals with more severe forms of aortic stenosis [76]. Right heart obstruction, including pulmonary valvar, subvalvar or supravalvar stenosis, atresia, or obstruction or tricuspid valve stenosis may also indirectly impact LV filling and CO, particularly when severe [66, 77, 78].

Finally, cyanotic HD consist of lesions in which deoxygenated blood (systemic venous blood) mixes with the oxygenated blood of the left heart (pulmonary venous blood) typically within the heart leading to reduced systemic O_2 saturations [77]. Some of these lesions have been associated with poor fetal/neonatal outcomes [14] and increased risk for maternal morbidity and

mortality [19-21]. This includes pathologies such as tetralogy of Fallot, truncus arteriosus, transposition of the great arteries, and Ebstein's anomaly of the tricuspid valve. Most affected patients will have corrective procedures in early to mid-infancy and others in young childhood [79]. Some, however, may have residual pathology in adulthood that could impact their pregnancy. For example, while individuals with corrected tetralogy of Fallot are usually able to progress in their pregnancy, pulmonary regurgitation, which is common long-term, could result in an additional burden to their right heart. Some also have fibrosis of the LV which could directly interfere with LV filling [1, 66]. Additional right ventricular outflow or branch pulmonary obstruction could contribute additional burden, impacting the right heart and indirectly left heart output, and thereby contribute to complications [80, 81]. Less commonly, cyanotic CHD patients have a functional single ventricle which is associated in infancy and early childhood with persistent right to left shunting and chronic hypoxemia (low O_2 saturations circulating in the blood). The hypoxemia ultimately is corrected with the Fontan procedure [82]. This procedure consists of rerouting the systemic venous return through an external conduit or an intracardiac (right atrial) baffle to the lungs, separating the systemic and pulmonary circulation [83]. Although some patients who are status post-Fontan procedure can complete their pregnancy, they might be limited in their ability to augment the CO due to absence of a pumping chamber ejecting blood into the pulmonary circulation, and are even susceptible to miscarriage in their first trimester of pregnancy [84].

Acquired Heart Disease: According to the Canadian Cardiac Disease in Pregnancy study, less than a third of MHD represents AHD. Two of the most commonly encountered forms of AHD in pregnancy include rheumatic heart disease and cardiomyopathy [13]. Rheumatic heart disease occurs as a complication of rheumatic fever, an inflammatory condition that evolves in response to a beta-

hemolytic streptococcal infection of the heart [85]. It is normally localized to the valves, mitral stenosis being the most common manifestation [86]. With pregnancy-related demands, mitral stenosis may prevent the necessary increase in LV preload and CO and higher heart rates limit the time of the heart to fill, also problematic for patients with mitral stenosis. This pathophysiology is also associated with increasing left atrial pressures leading to symptoms of heart failure and even atrial arrhythmias such as fibrillation [87, 88]. The condition might worsen throughout pregnancy even when the individual was healthy and asymptomatic in the preconception period [66, 89]. Cardiomyopathy is another type of "acquired" heart disease which affects the myocardium and can be congenital or acquired [90]. Primary cardiomyopathies may have different or even mixed phenotypes including hypertrophic, dilated, noncompaction or restrictive, and most often have a genetic underpinning [91]. One cardiomyopathy unique to pregnancy is that of peripartum cardiomyopathy which may manifest only in the last month of pregnancy or the first few months postpartum. The latter can be genetic and represent underlying myocardial disease only manifested through the demands of pregnancy and acute changes in afterload in the postpartum period, or might relate to pregnancy hypertensive disorders [92, 93]. Cardiomyopathies can also be secondary to adverse exposures, most commonly infection, that leads to myocarditis and, in some, permanent damage to the myocardium, and exposure to chemotherapeutic agents, particularly anthracyclines, that cause damage to the myocardium [94, 95]. In pregnancy, some of the complications related to cardiomyopathies might only become evident in the third trimester [90], and although CHD is more common than AHD in pregnancy [13], the latter appears to be associated with highest risk for mortality among mothers [7, 96].

Risk Classification Systems:

Various risk classification systems have been developed to anticipate risks for different types of MHD. These include classification based on cardiac symptoms (NYHA Classification) [35], maternal cardiac outcomes (CARPREG 1 and 2 classification systems) [13, 34] and risk of maternal mortality and morbidity (mWHO) [19-21] (Table 1-1). Maternal morbidity in the mWHO classification system includes the occurrence of heart failure, embolisms, preeclampsia, ventricular fibrillation, sepsis, or any complications that could be related to the MHD [97]. Another classification system, the Bethesda classification system [22, 68], has sometimes been used to assess the severity of CHD, but is not specific to pregnancy and does not include AHD. Although not perfect at predicting risk perhaps due to the lack of incorporation of other contributing factors such as cardiovascular coupling (i.e. VAC), these classification systems incorporate clinical risk factors including ventricular dysfunction, lesion-specific structural alterations, and state of the MHD lesion (repaired vs unrepaired) which provide some information about expected maternal health throughout pregnancy. However, none of these risk stratification systems include adverse fetal/neonatal outcomes which have been seen to occur in MHD [20] and more often in certain types of MHD [14]. The following section will therefore evaluate fetal/neonatal complications that have been reported in MHD in addition to cardiac and obstetrical complications to gain further understanding of the risks this population might encounter throughout pregnancy.

Table 1-1: Various Maternal Heart Disease Risk Stratification Systems			
Risk Stratification System	**Risk Factors and Considerations**	**Assessment**	**Pregnancy specific?**
NYHA [35]	Symptoms (i.e. shortness of breath, palpitations, fatigue)	Class of heart failure or cardiac condition	No
CARPREG I & II [13, 34]	Previous cardiac history including NYHA class, cyanosis, type of MHD, ventricular function status	Risk of maternal cardiac complications	Yes
mWHO [19-21]	Medical condition: type of MHD, state of MHD lesion (repaired vs unrepaired), ventricular function, aortic dilation	Risk of maternal morbidity and mortality	Yes
Bethesda [22, 68]	Anatomic complexity or structural pathology	Severity of CHD	No
NYHA: New York Heart Association; CARPREG: Cardiac Disease in Pregnancy Study; mWHO: Modified World Health Organization; HD: heart disease; CHD: congenital heart disease.			

Cardiac, Obstetrical, Fetal and Neonatal Complications in MHD

Cardiac Complications:

Cardiac complications in pregnancy are common in both CHD and AHD, especially arrhythmias and clinical heart failure [7, 90]. Hayward et al [98] saw an increased incidence of congestive heart failure in pregnancies with CHD at the time of delivery compared to those without CHD. They identified an odds ratio of 9.7 [95% CI: 4.7-20.0], $P < 0.001$ for non-complex CHD and an odds ratio of 56.6 [95% CI: 17.6-182.5], $P < 0.001$ for complex CHD (i.e. hypoplastic left heart syndrome/single ventricle, tetralogy of Fallot, transposition of the great arteries, truncus arteriosus). In addition, they saw an association between complex CHD lesions with the presence of serious ventricular arrhythmias and maternal mortality. Long-term, adverse cardiovascular outcomes have also been reported post-pregnancy in individuals with MHD. This was observed

by Siu et al [99] where hypertension was evaluated over a period of 90 days to 26 years after delivery in individuals with and without MHD. Hypertension (post-pregnancy) occurred in 24% of women with MHD compared to 14% in control pregnancies without MHD. Also, the incidence of hypertension after pregnancy was associated with higher risk of cardiac death and cardiovascular complications as depicted by an adjusted hazard ratio of 1.54 [95% CI: 1.05-2.25]. One could hypothesize that given those with MHD have a higher incidence of postpartum hypertension, they could indirectly be more at risk of adverse cardiovascular events after pregnancy. In addition to cardiac complications during and after pregnancy, MHD has been associated with additional obstetrical adverse outcomes.

Obstetrical Complications

Prevalent obstetrical complications among pregnancies complicated by MHD include preeclampsia, hemorrhage, and placental abruption [76, 100] all of which can vary with the type of MHD. In a literature review, Drenthen et al [14] saw an occurrence of thromboembolic complications in 2-19% and hypertensive disorders including preeclampsia in 2-16% of mothers with MHD compared to expected rates for healthy pregnancies that were close to 0% and 8% respectively. The highest rate of preeclampsia was among those with transposition of the great arteries, and pulmonary atresia with ventricular septal defect. They also observed a higher occurrence of pregnancy-induced hypertension among those with coarctation of the aorta, transposition of the great arteries and especially those with aortic stenosis [76]. Other lesions that have been reported to promote hypertension during pregnancy include valvular disease and cardiomyopathies. In fact, they appear to be among the types at the highest risk of obstetrical

complications. Minhas et al [100] observed an odds ratio of 1.9 [95% CI: 1.8-2.2] for preeclampsia, 1.4 [95% CI: 1.2-1.6] for intrapartum or postpartum hemorrhage, 1.3 [95% CI: 1.0-1.7] for placental abruption and 17 [95% CI: 13-22] for pulmonary edema in a cohort with valvular disease. In addition, Owens et al [101] reported an odds ratio of 5.1 [95% CI: 3.0-8.6] for preeclampsia in cardiomyopathies. It has also been reported that in severe cardiomyopathies, including peripartum cardiomyopathy, the occurrence of maternal mortality can be up to 50% [91]. Other types of MHD that have been found to have specific complications. Balci et al [102] observed that despite corrective surgery in childhood, 19% of pregnancies with tetralogy of Fallot suffered from miscarriages. In addition, the presence of cyanosis alone has been shown to promote adverse obstetrical outcomes. Siu et al [69] saw an odds ratio of 39 [95% CI: 9-174] for postpartum hemorrhage among those with MHD and related cyanosis. It is important to note that generally CHD pregnancies also have higher rates of cesarian sections than those without HD [103]. Some of these are performed for medical indications due to altered hemodynamics such as valvular regurgitation or high risk of arrhythmia [102]. However, for many this is a choice made by the obstetrical personnel often based on concerns about pre-existing cardiac conditions (i.e. structural cardiac disease) and how they might contribute to maternal complications rather than medical emergencies [104].

Fetal and Neonatal Complications

Generally, there is a frequency of 15-25% for spontaneous abortion in individuals with MHD depending on the type of cardiac disease compared to roughly 10% in the general population [14, 16, 17, 20, 105]. Overall MHD pregnancies have also shown a higher occurrence of premature birth (20.8% [16] vs ~11% [14] in pregnancies without HD) which can vary according to MHD lesion (6-65%) [14]. In the literature review by Drenthen et al [14] premature birth was prevalent among those

with cyanotic MHD (i.e. Fontan and transposition of the great arteries) but was also found in those with milder MHD (i.e. atrial and ventricular septal defects) to a lesser extent (6-12%). Valvular disease and cardiomyopathy have also been associated with an increased risk of premature birth [25]. In fact, it has been observed that 25.2% of pregnancies with cardiomyopathy present with premature birth compared to 14.2% when all types of MHD were pooled together and 5.5% in pregnancies with no HD [101]. Although some MHD lesions have a lower incidence of premature birth, MHD still predisposes infants to long lasting adverse outcomes as prematurity includes risks of pulmonary, brain, gastrointestinal and cardiovascular complications in the offspring [20, 16, 106].

Fetal growth restriction and consequent small for gestational age newborns are also prevalent in MHD (2-67% vs ~10% in pregnancies without HD) [14] which might contribute to a perinatal mortality that is 4-fold higher than the general population. [14, 16, 20, 23, 107]. Small for gestational infants, as depicted by lower birth weights, which are often associated with earlier delivery, have been seen more often among those with cyanotic MHD including those with a functional single ventricle status post-Fontan, but also among those with pulmonary hypertension, repaired tetralogy of Fallot and cardiomyopathy [14, 108]. Tetralogy of Fallot alone has previously been associated with an incidence of 19% for small for gestational age infants, 18% for preterm birth and 6.4% for fetal mortality [102]. In pregnancies with cardiomyopathy, small for gestational age newborns have been observed in 19.1% of pregnancies compared to 9.9% of all HD and 3.3% with no HD [101].

Other types of fetal and neonatal complications have been observed in a cohort of various MHD lesions including atrial/ventricular septal defects and more complex types including left heart obstruction, tetralogy of Fallot, Fontan physiology and transposition of the great arteries. This has included an incidence of respiratory distress syndrome in 8.3%, intraventricular

hemorrhage in 1.4%, intrauterine fetal demise in 2.8% and neonatal death in 1.4% [16]. Finally, fetuses, and neonates of individuals with MHD are also at risk of recurrence or inheritance of CHD ranging from 3-50% depending on the type of CHD [13, 20, 23, 109], and, in those with genetically inherited cardiomyopathies, this can also be passed to their offspring [110].

Although maternal and fetal/neonatal complications are most prevalent among those with complex forms of MHD (i.e. single ventricle/Fontan physiology, transposition of the great arteries, tetralogy of Fallot, cardiomyopathy and severe outflow obstruction), a predisposition for complications, albeit lower, is still present in those with milder disease (i.e. ventricular septal defect and mild aortic valve disease) which could increase depending on the state of MHD (i.e. repaired vs repaired and hemodynamic profile) [19-21, 68]. While there is still more to be understood regarding the role different pathophysiologies play in the adverse obstetrical and neonatal outcomes, some investigators have begun to explore responsible mechanisms for these complications. The next section will provide a deeper review of the current research and a description of the mechanisms that, to date, have been associated with poor outcomes in MHD.

Possible Cardiac Mechanisms Mediating Complications in MHD

Past studies have begun to explore cardiac factors that contribute to adverse maternal and fetal/neonatal outcomes in MHD. The presence of systemic hypertension in MHD [111, 112] is one such factor with certain MHD more predisposed to its presence and development in pregnancy. In aortic stenosis, for instance, there can be fibrosis and calcification of the valve which some argue might promote an inflammatory response, leading to vascular changes which could increase arterial blood pressure concomitantly with aortic stenosis [113]. Coarctation of the aorta can also be associated with hypertension, worse in the upper body when there is residual obstruction. Although

this can be managed, it could result in lower body hypotension interfering with blood flow delivery to the uterus and thus fetus [66].

Reduced CO has also been suggested to contribute to fetal/neonatal complications associated with MHD [25, 26]. Wald et al [26] demonstrated a similar CO between pregnant individuals with and without MHD. However, when comparisons were performed between MHD pregnancies with and without neonatal complications, including those with low birth weight and premature birth, the change in CO throughout the progression of pregnancy from baseline (≤26 weeks) through the third trimester was reduced in MHD with complications and significantly different from MHD without complications (Δ CO per unit time (L/week) : -0.01±0.10 vs 0.04 ±0.09).

Eggleton et al [25] also observed a lower CO (P=0.01) in late pregnancy (>28 weeks) in MHD pregnancies with versus without adverse neonatal outcomes (5.11±1.02 vs 5.77±0.94 L/min). Heart rate was similar among groups (84 ±13 vs 83±15 beats/min), however both average S' (8.67 ±1.88 vs 9.95 ±1.84 cm/s) and stroke volume (61.66±14.56 vs 70.88±13.92 mL) were significantly lower (P<0.05) in the adverse neonatal outcome group, suggesting cardiac functional parameters could be contributory. Average S' refers to the averaged septal and lateral mitral valve annular velocities during systole. Although not a perfect measure of systolic function given its load dependence (i.e. affected by both preload and afterload), its reduction was suggested to potentially indicate irregularities in the motion of the myocardial wall [114]. S' has previously been correlated with LVEF [115, 116], which could perhaps be contributing to reduced CO in those with adverse neonatal outcomes. Given that stroke volume is highly dependent on loading conditions, contractility as well as the diastolic function of the myocardium, one or more of these factors could be affected in MHD reducing the stroke volume, and, consequent CO [117]. In some forms of MHD

such as in aortic stenosis, afterload is increased which can affect stroke volume as the heart has to work harder against the valve to eject. This can ultimately lead to LV remodeling including hypertrophy and fibrosis [118] affecting LV diastolic function and contractility [119]. This reduction in contractility can also be observed in other forms of MHD, especially in cardiomyopathies and those who have developed LV hypertrophy [120, 121] , as it has been shown that the myocardium in these conditions produce less force perhaps due to contractile abnormalities or reduced myofibril density [120].

Although no significant differences were detected in global longitudinal strain between groups by Eggleton et al [25], one could hypothesize that reduced contractility could contribute to reduced CO in these complicated pregnancies. This was supported by an observed association between global longitudinal strain and birth-weight centile (R^2=0.11, P=0.04) where a larger degree of strain was associated with increased birth-weight centile in MHD. CO was also associated with birth-weight centile (R^2=0.18, P=0.0002), making an important link between maternal heart health and blood delivery to the fetus. Taken together these findings suggest that reduced cardiac function as depicted by reduced stroke volume, perhaps as a result of reduced contractility, could contribute to reduced CO which plays an important role in negatively impacting fetal well-being. However, further investigations are necessary to establish these associations.

The Placenta and Uteroplacental Circulation in Heart Disease

In addition to poor cardiac function, there are other downstream factors, such as an altered uteroplacental circulation, that could be contributory especially to fetal and neonatal complications in MHD. For instance, the heart will initiate the flow of blood to the rest of the body which will

eventually reach the fetal circulation through the uterus and placenta [122]. However, abnormalities of the uteroplacental circulation could prevent sufficient delivery of oxygenated blood to the fetus. The exact etiology for altered or reduced uteroplacental flow is still unclear, however, some suggest that it could be related to maternal cardiac dysfunction [123]. Therefore, it is important to analyze the uteroplacental circulation in MHD to gain further understanding as to how altered cardiac function and perhaps maternal CO may relate or even contribute to altered placental health and fetal development. This might also shed light on other mechanisms that could be contributing to poor maternal, fetal, and neonatal outcomes in MHD.

The placenta is a critical organ that evolves for the sole purpose of providing nutrients and oxygen to the growing fetus through a low-resistance circulation [124]. The placenta consists of a maternal (basal) and a fetal (chorionic) side with an intervillous space in between. This space is where spiral arteries carrying oxygenated maternal blood will perfuse the intervillous space of the placental cotyledons composed of chorionic villi [122]. The villi will then carry the oxygen and nutrient-rich fetal blood to the umbilical vein to reach the fetal circulation [124-126]. Decreased uteroplacental flow and placental function contributes to intrauterine growth restriction and consequent small for gestational age at birth as well as preterm birth, both fetal/neonatal complications associated with MHD [14, 127-129].

There are clinically applied ultrasound-based methods to identify placental flow and functional abnormalities. Flow patterns in the umbilical (UA) and uterine (UtAs) arteries have systolic and diastolic periods. A commonly applied Doppler-based measure of flow is the pulsatility index (PI) [130] which is the ratio of the difference between the peak systolic velocity and end-diastolic velocity by the average maximum velocity. This is a measure of the differences in resistance between upstream and downstream vascular beds [131-133]. In normal pregnancies, both

the UA and UtAs will start with a high PI and will decrease as pregnancy progresses [134, 135]. For the UA, it has been suggested that the progressive decrease in resistance is due to novel angiogenesis within the placenta that occurs with increasing gestational age, with a significantly increased rate of angiogenesis starting at the 25th week of pregnancy [136-138]. Given the increased branching and the presence of new vessels, resistance to flow decreases [136, 139]. For UtAs, flow patterns are affected by uterine spiral artery remodeling [140, 141]. Before pregnancy, spiral arteries (through the radial arteries) are an extension of the UtAs that will sit at the myoendometrial junction and will provide oxygenated blood to the uterus [142]. Around 12 weeks of gestation, trophoblasts, a type of cell originating from the fertilized egg (blastocyst) [124], will invade a layer of the endometrium called the decidua [143]. This invasion and remodeling, which is completed by midgestation [141, 144], will lead to the transformation of spiral arteries from small high-resistance to larger low-resistance vessels allowing for increased blood flow [145, 146]. This will contribute to a progressive decrease in resistance.

As mentioned earlier, UA and UtA Doppler flow patterns provide information about both systolic and diastolic velocities which infer information about upstream and downstream vascular resistances [130]. For instance, in the setting of placental pathology with high placental resistance, reduced, absent or reversed end-diastolic velocities have been observed in the UA [147]. Furthermore, abnormal flow patterns as depicted by an increased PI of the UA can indicate an abnormal fetal-placental circulation or higher placental impedance/resistance to blood flow downstream which could contribute to intrauterine growth restriction, and small for gestational age fetuses [127, 134, 148, 149]. Through a computer-based model, Surat el al [150] suggested that placental resistance and UA radius affect UA PI. However, the elastic properties of the UA wall have a far lesser effect. On the other hand, in UtA Doppler waveforms, an early diastolic notch (i.e. the reduced velocity

immediately after the systolic flow but before the maximal diastolic flow), after the first trimester has been considered an abnormal flow pattern [151, 152]. A persistent notching has been suggested to reflect unusual maternal vascular tone and abnormal placentation [152, 153]. Adamson et al [154] showed through a computer-based model that UtA PI increased with increasing uteroplacental resistance and reduced UtA radius. However, changes in mean arterial pressure in the UtA did not significantly affect the PI, suggesting that UtA PI is primarily affected by innate vascular properties such as resistance and diameter. UtA PI is clinically helpful as it can identify maternal vascular malperfusion of the placenta and is predictive of preeclampsia [155, 156]. It is believed that maldevelopment of spiral arteries and poor trophoblast infiltration of the placenta will increase resistance to blood flow (increased UtA PI) in the vasculature resulting in hypoperfusion [149, 157-159] which can then culminate in various fetal and neonatal complications.

Some have seen an association between cardiac dysfunction, and abnormal uteroplacental Doppler flow patterns in patients with MHD [26, 160]. Kampman et al [161] conducted a systematic review analyzing the association between maternal cardiac function during pregnancy (11-33 weeks) in those with and without known MHD. Abnormal uteroplacental flow patterns, suggesting higher resistance to flow, were found to be associated with heart dysfunction in both groups. For instance, there was a significantly lower CO in pregnancies with abnormal UtA waveforms that had complicated outcomes compared to those with normal uteroplacental Doppler waveforms or those with abnormal UtA with uncomplicated outcomes. Although the underlying cause of abnormal uteroplacental flow patterns due to cardiac dysfunction was not fully confirmed by this association, Kampman et al suggested that cardiac dysfunction could affect placentation and therefore the uteroplacental circulation as depicted by higher resistance to flow (i.e. higher UtA PI).

MHD pregnancies have been reported to have a higher occurrence of abnormal uteroplacental waveforms [160-162]. Suboptimal maternal cardiac function, such as could occur in some types of MHD [66], could cause a reduction in maternal CO which could ultimately lead to abnormal uterine blood flow patterns and reduced blood flow to the placenta [26, 123, 163, 164]. This, in turn, could culminate in placental hypoperfusion leading to placental and consequent fetal underdevelopment [161]. This relationship between maternal CO and fetal well-being in MHD was further supported by the work of Wald et al [26] . They witnessed a reduction in CO as pregnancy progressed in MHD pregnancies with neonatal complications compared to an increase in CO observed in MHD pregnancies with no neonatal complications. They found that the MHD group with neonatal complications showed higher resistance or bilateral notching in the UA and UtA Dopplers more often in the third trimester than MHD pregnancies without neonatal complications. Given that higher resistance in the UtAs could reduce blood flow to the uterus, fetal growth could be compromised which could contribute to growth restriction and premature birth. CO was not different between all MHD and control (no MHD) pregnancies and UtA PI decreased in both controls and MHD patients as pregnancy progressed. However, UtA PI remained higher in the third trimester in MHD pregnancies compared to controls (0.87±0.23 vs 0.79±0.19, P=0.038) suggesting increased resistance to flow in MHD. These findings suggest an association between MHD and increased UtA resistance where MHD can still affect the uteroplacental circulation despite a grossly preserved CO. Pieper et al [160] also evaluated UA and UtA Doppler flow parameters which included the resistance index (RI) (the difference between peak systolic velocity and end-diastolic velocity divided by peak systolic velocity) [133] as well as PI at 20 and 32 weeks in MHD. Although PI and RI decreased in the UA and UtAs as pregnancy progressed in both controls and MHD individuals, the MHD group had a greater UtA PI than healthy controls even

as early as 20 weeks ($P<0.05$), and UA PI and RI were higher in MHD than controls at 32 weeks ($P<0.05$). This could suggest altered placental vascular health can be manifested later in pregnancy in MHD, perhaps due to initial abnormalities in placentation. They also found the MHD cohort to have a higher incidence of preeclampsia and early rupture of membranes, and offspring complications including small for gestational age newborns.

Others have also suggested that compromised placental development in MHD could contribute to impaired or abnormal UA and UtA blood flow [108, 165]. Wu et al [166] analyzed placentas from women presenting with a variety of cardiovascular diseases including general CHD, various types of cardiomyopathies, connective tissue, and valvular disease. In general, 75% of placentas presented some type of abnormality with 27% of the placentas in this cohort being small. Other observations included abnormalities in umbilical cord insertion and implantation of the placenta, as well as a prevalence of 11% for inflammatory pathologies. However, a very important finding was that a large proportion (41%) of the placentas demonstrated vascular pathology, with 26% showing signs of maternal vascular malperfusion, a finding that supports a contribution from inadequate maternal cardiovascular support of the placenta. Clearly, there is much to consider about the origins of abnormal UA and UtA Doppler flow patterns in the MHD population and how they can contribute to poor fetal and neonatal outcomes. Given that the heart and vascular system are intimately connected, insufficient flow or increased resistance to flow in the placenta could also be due to innate vascular dysfunction in the mother.

Vascular Dysfunction in Heart Disease

The vascular system plays an important role in the adequate progression of pregnancy as it can either facilitate or restrict the delivery of blood to the mother's organs, including the uterus

and, consequently, the fetus. In MHD, however, vascular health, and therefore the ability of vessels to deliver blood in an efficient manner, might be compromised [167, 168] as vascular health, arterial stiffness and endothelial function, have been reported to be affected in various forms of CHD [169].

Arterial Stiffness in CHD

Increased arterial stiffness has been documented in a systematic review by Sandhu et al [27] in individuals with transposition of the great arteries, coarctation of the aorta, tetralogy of Fallot and single ventricle. In addition, in a comprehensive systematic review and meta-analysis recently conducted by our team [169], various parameters of arterial stiffness were found to be increased from an early age (starting at 6.5 years) in individuals with CHD compared to those without. We detected an increased augmentation index (large effect size; SMD: 1.06, 95% CI: 0.73, 1.39), an indicator of wave reflection in the vessels due to vascular stiffness [170] compared to controls ($P<0.00001$). Pulse-wave velocity, an indicator of pressure wave propagation as a result of vessel distensibility and compliance, and lower arterial distensibility [171], which increases with increasing vessel stiffness [172], was also higher in CHD than controls ($P<0.00001$) as depicted by an effect size (SMD) of 0.58, 95% CI:0.42, 0.75). The values were particularly higher in individuals with more complex CHD such as transposition of the great arteries and tetralogy of Fallot, common forms of CHD present in MHD populations. Therefore, various parameters of vascular health are known to be adversely affected in individuals with CHD, all despite early repair. Thus, one could hypothesize that perhaps the deterioration of vascular health as a consequence of CHD could predispose these individuals to complications during pregnancy if they impair the ability of the vascular bed to adapt with pregnancy progression.

Endothelial Function in CHD

Our team [169] also examined the evidence for endothelial dysfunction in the CHD population. We observed decreased metrics for endothelial-dependent dilation including decreased flow-mediated dilation and reactive hyperemia, [173]. Flow-mediated dilation was particularly lower in those with more complex forms of CHD including tetralogy of Fallot, Fontan and single ventricle physiology and coarctation of the aorta compared to healthy controls. Even children with CHD displayed endothelial dysfunction. The mechanisms mediating dysfunction at the level of the endothelium in CHD are still a topic of debate. However, alterations of arterial structure affecting dilatory properties such as increased collagen and reduced smooth muscle mass [174], as well as reduced NO bioavailability [175, 176] have been proposed to be contributory. This has been observed in pediatric patients post-CoA repair where endothelial dysfunction was observed in conjunction with vascular wall alterations [177]. In patients with cyanotic CHD, it has been proposed that the prolonged exposure to hypoxia could promote increased permeability of the endothelium, as well as increased inflammation and reduced anticoagulation properties [178, 179]. Therefore, one could hypothesize that various MHD pregnancies have underlying endothelial dysfunction which could impair the necessary vascular adaptations of pregnancy.

Possible Arterial Stiffness and Endothelial Dysfunction in MHD

The results above suggest that increased arterial stiffness, endothelial dysfunction or both might be present in MHD. Even in pregnancies without MHD there has been an association made between vascular dysfunction and some of the adverse obstetrical and fetal/neonatal outcomes

found in MHD [28, 29, 180]. Therefore, poor vascular health is a potential contributor to poor maternal, fetal, and neonatal health outcomes in MHD.

As mentioned previously, increased arterial stiffness is commonly observed in CHD. Increased arterial stiffness results in an increase in blood pressure and subsequent risk of hypertension [181, 182]. In addition, increased stiffness in conduit vessels and large arteries promotes the remodeling of small arteries which can lead to increased vascular resistance [183]. Given that normal adaptations in healthy pregnancy involves a reduction in vascular resistance and subsequent maintenance or decrease in blood pressure in the context of increased blood volume [6], arterial stiffness as a result of long-standing CHD could promote hypertensive complications such as preeclampsia [184]. While not previously explored in MHD pregnancies, evidence for this association has been found in pregnancies without MHD. Yinon et al [184] , for instance, found metrics of increased arterial stiffness among postpartum women without MHD (6-24 months after delivery) with a history of preeclampsia. In fact, significantly higher values for augmentation index ($P<0.008$) were seen in those with a history of early-onset preeclampsia (27.8±5.3) compared to healthy controls (15.1±8.9), perhaps suggesting that the presence of preeclampsia might due to underlying increased arterial stiffness [181, 182]. Arterial stiffness could also contribute to fetal/neonatal complications including fetal growth restriction [185]. For instance, increased vascular resistance in the uteroplacental circulation impedes blood flow to the fetus which can ultimately result in restricted fetal development [160, 186]. Yinon et al [184] found individuals with normotensive pregnancies but with intrauterine growth restriction (28.7±5.7) to have a significantly higher augmentation index ($P<0.008$) than healthy control counterparts (15.1±8.9). These findings were further corroborated by the work of Tay et al [185] , where augmentation index and pulse-wave velocity were higher among pregnancies presenting with preeclampsia and fetal growth restriction,

preeclampsia without fetal growth restriction and normotensive pregnancies with fetal growth restriction compared to healthy controls with normally grown fetuses. Although the latter team found CO to be significantly lower among those with preeclampsia and fetal growth restriction; the cause for this reduction was not explored. Nevertheless, these findings suggest that increased arterial stiffness in pregnancy likely underpins poor obstetrical, fetal, and neonatal outcomes, and may be true of MHD.

Endothelial dysfunction has also been proposed to contribute to obstetrical complications in pregnancy such as preeclampsia [180]. The endothelium detects increases in blood flow and promotes vasodilation to accommodate [187]. This is achieved by the release of nitric oxide, an important vasodilator [188]. However, this has been shown to be impaired in pregnancies with preeclampsia where there is a reduction in nitric oxide release and subsequent potential for vasodilation [180, 189, 190]. Yinon et al [184] evaluated vascular function with flow-mediated dilation in pregnancies with a history of early and late-onset preeclampsia as well as intrauterine growth restriction without preeclampsia in the post-partum period. Endothelial dysfunction was defined as a value <4.5% for flow-mediated dilation. They found significantly lower values for flow-mediated dilation ($P<0.0001$) in pregnancies with early onset preeclampsia (3.25±0.70%) and those with intrauterine growth restriction alone (2.14±0.44%) when compared to control individuals (9.14±0.90%) and those that had late onset preeclampsia (7.93±1.33%). Endothelial dysfunction was particularly important among individuals with concomitant early onset preeclampsia and fetal growth restriction with a mean value of 2.4±1.3% for flow-mediated dilation. Given that preeclampsia and fetal growth restriction are complications often seen in MHD, endothelial dysfunction which may therefore not promote vasodilation and reduced

systemic vascular resistance needed in pregnancy[191], might be a contributing factor in MHD populations.

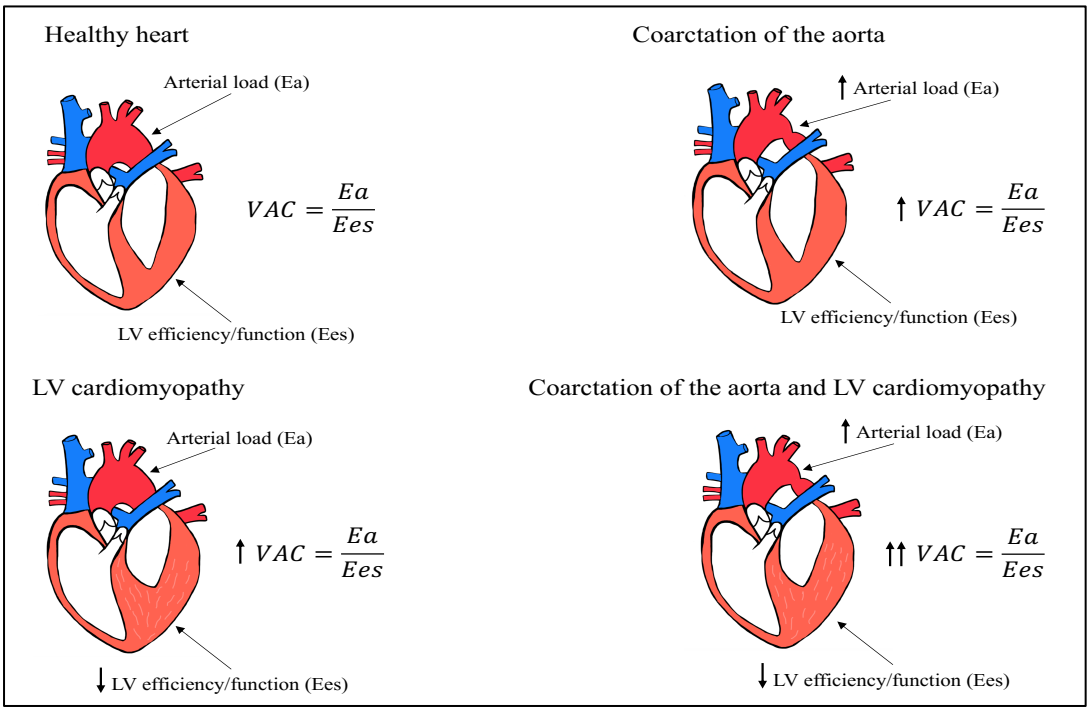
In brief, the current review suggests that various obstetrical, fetal, and neonatal complications in MHD could be a result of cardiac dysfunction, altered vascular health or both. An integrated understanding of both cardiac function and vascular health in MHD would therefore provide important insights on mechanism mediating complications in this population. This can be achieved with an important evaluator of overall cardiovascular health that includes arterial load, which changes with increased arterial stiffness [31], and LV efficiency which is a determinant of cardiac function, also known as ventricular-arterial coupling or VAC [30]

Ventricular-arterial coupling (VAC)

The heart and vascular system must work together in pregnancy to ensure proper oxygen delivery to the maternal organs and the fetus. The LV is responsible for pumping oxygenated blood to the whole body and must work against the vascular system. The vessels can act as an opposing force or load depending, in part, on the amount of vascular resistance to flow [192] which can affect LV performance or the amount of work it must perform to sustain a proper CO [193] . The manner in which the LV and the arterial system work together is called ventricular-arterial coupling (VAC) and it is a measure of cardiovascular performance [194]. In fact, VAC has been recognized as an important player in cardiovascular disease and has been reported to be a good surrogate to assess severity in various types of cardiovascular disorders [195]. Therefore, understanding its role in pregnancy and MHD could allow for the identification of cardiovascular problems and their relation to poor pregnancy, fetal and neonatal outcomes. There is a numerical evaluation that

allows for the study of VAC, and it can be obtained through the ratio of arterial elastance (Ea) and end-systolic elastance (Ees). Ea simply represents the force opposing the LV, also known as the arterial load, and Ees is a representation of LV cardiac efficiency or function. Ea is the ratio between the end-systolic pressure and stroke volume. The calculation of Ees includes, but is not limited to the ejection fraction, stroke volume and diastolic and systolic blood pressures [30, 196]. Therefore, a greater value for VAC (Ea/Ees) suggests increased arterial elastance (load), decreased end-systolic elastance (efficiency/function) or both [30] (Figure 1-2).

Figure 1-2: Examples of Altered Ventricular-Arterial Coupling



Ea: arterial elastance (arterial load); Ees: end-systolic elastance (LV efficiency/function); LV: left ventricle.

Given that several adaptations take place during pregnancy including reduced mean arterial pressure and vascular resistance [6] and increased preload [57], one could hypothesize that VAC will change during pregnancy. Currently, there is limited literature and some have debated on the

effects of pregnancy on VAC. However, Estensen et al [197] showed that VAC increased in each of the three trimesters of pregnancy, most significantly in the last (0.64 ±0.23, P<0.01) relative to the first and second trimesters (0.45±0.14, 0.53 ±0.17) respectively. The mechanisms mediating this increase in VAC are unclear, but it was postulated that it could relate to decreased LV contractility which would decrease Ees. Although, arterial load decreases throughout pregnancy as depicted by a decrease in vascular resistance relative to pre-pregnancy, the arterial load might still be greater than the ability of the myocardium to contract, at least for a given stroke volume [57, 197] which could explain the increase in VAC as pregnancy progresses. Others have observed no significant change in the evolution of VAC in pregnancy [58, 198] leaving room for debate as to whether VAC changes with increasing demands (i.e. increase in CO) in each subsequent trimester.

Knowledge as to the direct impact of MHD on VAC is also quite limited. A single study, that of Muneuchi et al [33], assessed VAC in 31 pregnant individuals with CHD in the first and second trimesters and found both Ea and Ees were decreased as pregnancy progressed, allowing for a preserved VAC throughout pregnancy. The results suggested that both arterial load and LV function or efficiency decreased simultaneously, maintaining the same VAC in MHD. Arterial load might have decreased due to decreased blood pressure and vascular resistance as part of normal cardiovascular adaptations in pregnancy [6]. Perhaps LV efficiency (Ees) decreased due to underlying cardiac dysfunction as a result of CHD [199]. However, this decrease in LV efficiency was not sufficient to increase VAC which might suggest preserved cardiovascular performance. Nevertheless, this study did not include control pregnancies, therefore, it is not known how VAC differs between MHD and control pregnancies. In addition, the cohort included were considered low risk for cardiac events [35]. Therefore, a more drastic change in Ees, which could increase VAC and affect overall cardiovascular performance, might only be observed in more severe forms of

MHD during pregnancy. In support, significant abnormalities of VAC have been previously observed in non-pregnant individuals with heart disease [199, 200]. In fact, in the work of Saiki et al [199] VAC was seen to be increased in a group of individuals with single ventricle/Fontan physiology. Ea was similar between the Fontan group and controls (1.35 ± 0.55 mm Hg/mL vs 1.33 ± 0.30 mm Hg/mL); however, Ees was significantly lower ($P<0.05$) in the study group than controls (1.39 ± 0.67 mm Hg/mL vs 2.37 ± 0.63 mm Hg/mL). This resulted in an increased VAC for Fontan patients compared to controls (0.95 vs.0.56, $P<0.05$). Given that the Fontan physiology can be present in MHD, this group of patients likely have altered VAC in pregnancy. However, given that the Fontan physiology is one of the most severe forms of CHD and MHD and less commonly encountered, less severe types of MHD should be further investigated to gain a deeper understanding of how MHD in general can affect cardiovascular coupling in pregnancy.

Ky et al [200] evaluated VAC in non-pregnant individuals with chronic systolic heart failure. Groups were formed based on the severity of the condition as determined by NYHA classification system where I was the least severe and IV was the most severe. Interestingly, Ea increased with increasing severity of heart failure and Ees decreased. This resulted in VAC values (mean (25^{th}, 75^{th} percentiles) of 1.55 (1.20, 2.24), 1.80 (1.36, 2.34), 2.10 (1.59, 2.67) and 2.46 (1.78, 3.41) for class NYHA I, II, III and IV respectively. Although heart failure represents more extreme cardiac pathology and might not be completely applicable to MHD, it provides some insight regarding how both Ea and Ees are altered in the setting of severe cardiac dysfunction. Given that VAC is an overall measure of cardiovascular performance [30] and it has been shown to change in various forms of cardiovascular disease [195] including CHD [199] and heart failure [200], one could hypothesize that VAC may be altered in MHD particularly with clinical cardiac dysfunction which might contribute to complications in these pregnancies. However, given the associated increase in arterial

stiffness, which could consequently increase load despite early lesion repair in CHD[169], even in the absence of overt cardiac dysfunction, altered arterial stiffness may also contribute to altered VAC in MHD.

In fact, changes in both Ea and Ees have been observed in a specific complication that has been reported in MHD, that is preeclampsia [20]. Yuan et al [201] found the ratio between Ea/Ees to not differ between pregnancies with preeclampsia without MHD compared to controls; however, both Ea (2.41 ± 0.57 mmHg/ml vs. 1.98 ± 0.46 mmHg/ml, $p = 0.0005$) and Ees (11.68 ± 9.51 m/s^2 vs. 6.91 ± 6.13 m/s^2, $P = 0.002$) parameters were higher in the preeclampsia cohort suggesting increased arterial load and increased LV function or efficiency. This study suggested in the absence of baseline myocardial disease, cardiac function may be able to meet the challenge of greater arterial load. However, if there is underlying even subclinical cardiac dysfunction in MHD, this may not be true resulting in altered VAC.

The exact etiology of the changes in VAC in MHD and normal pregnancy remains unclear. In addition, whether VAC is altered in MHD has not yet been fully explored. However, as either Ea or Ees disproportionately change, there will be a change in VAC. Given the current evidence of impaired vascular health in CHD [27, 169] and reduced cardiac function in some MHD pregnancies with complications [25, 26, 160], one could hypothesize that VAC might be altered by either changes in Ea, Ees, or both contributing to complications. As mentioned earlier in this review, MHD has been shown to be associated with cardiac dysfunction and abnormal UtA and UA Doppler flow patterns [161] which could contribute to poor obstetrical, fetal, and neonatal outcomes. Since VAC has been shown to be a good measure of disease severity and patient outcome for multiple conditions including hypertension and heart failure [195, 202, 203], its in-depth evaluation in MHD could provide insights of overall cardiovascular health in these pregnancies. The exploration of its

association with cardiac function and UtA and UA Doppler flow patterns could also provide insights on mechanisms that contribute to complications in these pregnancies and potentially prediction of poor obstetric, fetal, and neonatal outcomes.

Therefore, in the present investigation, we explored VAC in MHD and with concomitant assessment of cardiac function, the latter of which directly relates to the end-systolic elastance (Ees). The objectives of this investigation were to:

1. Compare VAC between pregnancies complicated by MHD and healthy controls in the midtrimester (18-24 weeks).
2. Compare measures of systolic (i.e. cardiac output, ejection fraction, contractility) and diastolic (i.e. E/E') LV function between MHD pregnancies and healthy controls in the midtrimester (18-24 weeks) and their association with VAC.
3. Explore the associations between UA and UtA Doppler flow patterns and VAC in the midtrimester (18-24 weeks) of pregnancy.

We hypothesized that:

1. VAC will be higher in pregnancies complicated by MHD than control pregnancies at 18-24 weeks and will be associated with reduced CO in MHD.
2. At 18-24 weeks, MHD will be associated with reduced LV systolic and diastolic function which contributes to reduced CO.
3. Higher UA and UtA PIs will be found at 18-24 weeks in MHD pregnancies compared to control pregnancies. Higher UA and UtA PIs will be found in MHD pregnancies that present with increased VAC.

The study of VAC and further exploration of LV function in MHD within this study will provide insights on cardiac mechanisms that might contribute to complications in MHD later in pregnancy. The findings of the present study will provide insight into whether VAC is altered in MHD, particularly in more severe MHD, as well as the underlying cardiac health in the midtrimester of pregnancies complicated by MHD. In addition, the exploration of UA and UtA PIs in MHD, concomitant with the evaluation of VAC and LV function could elucidate relationships between VAC and LV function in MHD that could ultimately contribute to altered fetal growth in the midtrimester and potentially later in pregnancy. Given that the number of MHD pregnancies is on the rise, understanding cardiac implications during this gestational period in this population could help identify specific aspects of cardiac function that could be targeted for future treatment development to help these individuals from an early age or in the preconception period through pregnancy. If in our work we find increased VAC but with intact LV function in our MHD cohort, this could direct future research into the association of vascular health and its contribution to adverse pregnancy outcomes.

CHAPTER 2: METHODS

This investigation explores ventricular-arterial coupling (VAC) and parameters of cardiac function in pregnancies complicated by maternal heart disease (MHD) with further study of the uterine-placental-fetal circulation and its relationship with VAC at 18-24 weeks of pregnancy. In the current chapter, the methodology will be reviewed including justification for specific approaches or techniques chosen for the investigation.

Study Design

This investigation represented a prospective cross-sectional clinical observational study in the midtrimester of pregnancy (18-24 weeks) of individuals with MHD in comparison to healthy control pregnancies.

Participants

Pregnant patients with MHD, including those with congenital (CHD) and acquired (AHD) heart disease, were recruited at the Maternal Heart Health Clinic and Fetal Echocardiography Laboratory within the Royal Alexandra Hospital, Lois Hole Hospital for Women, and the Mazankowski Alberta Heart Institute Adult CHD Outpatient Clinic. The inclusion criteria included pregnant women with MHD in the midtrimester of pregnancy (18-24 weeks). The midtrimester was selected as the timepoint of interest given that it is a period in which significant cardiovascular adaptations take place [6]. The range of 18-24 weeks of gestation was chosen in particular given this is in the early-mid aspect of the second trimester, and it is a usual time in which pregnant

individuals with MHD are screened by fetal echocardiography to exclude fetal cardiac disease as part of their routine clinical care, thus facilitating recruitment and participation.

Inclusion criteria for participants with MHD included: repaired, palliated or unrepaired CHD or AHD including rheumatic heart disease and primary or secondary myocardial disease (e.g. cardiomyopathy, ischemic heart disease, post-chemotherapy myocardial disease). Participants were excluded if they did not have CHD or AHD, if they had connective tissue disease only (e.g. Marfan syndrome), primary arrhythmias with a structurally normal heart, primary inflammatory disorders, were using immunosuppressant agents, had a multiple gestation pregnancy or a pregnancy complicated by fetal cardiac, chromosomal, or extra-cardiac anomalies which could independently impact the fetal circulation beyond fetal growth restriction or placental insufficiency given this is a known pregnancy complication in MHD .

Control participants included healthy women without MHD with uncomplicated pregnancies in the midtrimester (18-24 weeks) and no fetal anomalies, matched by age, pre-pregnancy body mass-index (BMI) and body surface area (BSA) at the time of the visit. For the purposes of this study, fetal and maternal echocardiograms were performed in both MHD and control pregnancies at 18-24 weeks. Control participants were recruited from the LHHW obstetrical clinics and the Program for Pregnancy and Postpartum Health as well as among the Stollery Children's Hospital staff and through word of mouth. Recruitment and enrollment were assisted by the research nurse on site (S.L). We excluded pregnant subjects without MHD with obstetrical risk factors or medical conditions that suggested that their pregnancy was not "low risk", such as gestational hypertension.

Approval to conduct this clinical research was provided by the University of Alberta Research Ethics Board (Pro00084169), and written informed consent was obtained from all participants prior to their participation. Additional operations approval was secured through Alberta Health Services clinical management teams as necessary.

Medical History

A medical history questionnaire was sent to participants upon recruitment into the study through the REDCap database (developed with support from the Women and Children's Health Research Institute (WHCRI)). Details with respect to medication use, comorbidities, past pregnancies, and deliveries as well as family history information were collected from the medical history questionnaires and confirmed with information from the electronic medical record when incomplete. This information was stored in the REDCap database to maintain patient confidentiality.

Medication use for all participants was recorded. No participants were excluded based on their medication use. Therefore, all medications were recorded and indicated in the analysis if the use was significantly different among groups or if the drug was known to directly affect the cardiovascular system. For some medications such as levothyroxine, warfarin and beta-blockers, medical history was reviewed for individual patients to better understand the indication for prescription.

Heart Lesion Severity Classification

Medical history consisting of previous cardiac interventions were evaluated for each patient by a cardiologist (LKH) and graduate student (JLM) to assess MHD severity and residual cardiac structural pathology post-intervention. Following review of the medical record, maternal cardiac status was categorized based on the modified World Health Organization (mWHO) classification system (www.ahajournals.org/doi/full/10.1161/cir.0000000000000458) [19-21] of maternal cardiovascular risk for exploratory lesion subgroup analyses. With the exception of very low acuity MHD (e.g. small, unrepaired VSD), who were not evaluated by the services, the mWHO category was routinely reported in clinic notes from the Maternal Heart Health Clinic and Obstetrical Medicine services. Although NYHA classes were available from medical history records, the NYHA [35] classification only focuses on symptoms of heart failure and is not specific to pregnancy. Other classification systems were available to categorize maternal cardiac status, but they had limitations and were therefore not utilized in our study. For instance, the Bethesda Classification system [22, 68] which considers cardiac structural severity, provides an assessment for CHD severity, but is not specific to pregnancy and excludes AHD. The CARPREG I & II evaluate risks for maternal cardiac complications but does not consider overall maternal morbidity or mortality. The mWHO classification system evaluates maternal mortality and morbidity risk related to specific cardiac lesions providing further insight on the MHD profile of the participants and therefore better risk and severity stratification for our cohort. Using mWHO, severity of MHD was generally classified into mild (mWHO categories I and II) and moderate-severe (mWHO categories II-III, III or higher) with modifications for some patients who had less or more significant residual lesions.

General Somatic & Cardiac Measures

Height, weight, blood pressure and heart rate were acquired for each participant. Height was provided by each participant. Weight was measured at the time of the visit and measured in kilograms with a manual physician scale on site. Three consecutive measurements of systolic, diastolic and mean arterial blood pressures were obtained with a digital blood pressure cuff after the patient had been resting for 15 minutes. An average of the three measures was calculated. In addition, the body surface area (BSA) for each participant was calculated at the time of visit by using the Mosteller formula [204] which includes weight (kg) and height (cm) and has been previously used in the literature as a standard measure [205]:

$$BSA\ (m^2) = \sqrt{\frac{Weight\ (kg)\ x\ height\ (cm)}{3600}}$$

Blood samples were taken to evaluate the levels of the N-terminal prohormone B-type natriuretic peptide (NT-proBNP), a biomarker of myocardial stress and heart failure, among participants. Patients did not fast beforehand. The B-type or brain-type natriuretic peptide is secreted mainly by the myocardium of the ventricle as a prohormone (proBNP) in response to myocardial wall stress. This peptide is subsequently cleaved in the circulation resulting in the active form of BNP and a more stable inactive fragment known as NT-proBNP [206]. High levels of NT-proBNP (>400 ng/L) are observed in the presence of ventricular dysfunction and heart failure [207-209]. The evaluation of this peptide was not used to classify patients according to their risk of heart failure, but rather to obtain an objective measure about the cardiac state at the time of the study.

Transthoracic Echocardiography

On the day of the assessment, participants were scheduled to come into the clinic in the morning or afternoon, depending on the schedule and availability of the fetal echocardiography clinic at the LHHW. Patients were not required to fast prior to the visit. Given that the patients were seen at the hospital, they were either registered in the Alberta Health Services Connect Care system as either research participants or clinical participants, if they had been scheduled for a fetal echocardiography for clinical indications such as MHD.

A transthoracic echocardiogram was performed using a Vivid IQ Echo System (General Electric Healthcare) with a 4MHz phased array transducer (M5Sc-RS General Electric Healthcare). The echocardiogram was performed by a trained sonographer or echocardiologist depending on availability at the time of visit. Interpersonal variability of image acquisition was controlled by following the same functional echocardiography protocol according to established American Society of Echocardiography guidelines [210, 211], as detailed below. For each 2D and color and tissue Doppler assessment, 3-5 beat clips were recorded. All pulsed Doppler based assessments included at least 3-5 consecutive tracings and measures represented an average of the three. Heart rate was monitored throughout the examination. Studies were stored as DICOM images on IntelliSpace Cardiovascular (ISCV) (Phillips) and ViewPoint 6 (GE Healthcare) for subsequent offline analyses.

JLM analyzed all the studies for the participants. She was trained by LKH and one of the lead sonographers (BH) to perform offline analyses. Given that JLM assisted with participant exam coordination during the appointments, she had access to participant information including their condition (i.e. control vs MHD) and ID number. The names and ID numbers for participants were necessary to access scans and to record data, therefore, complete blinding was not feasible as she

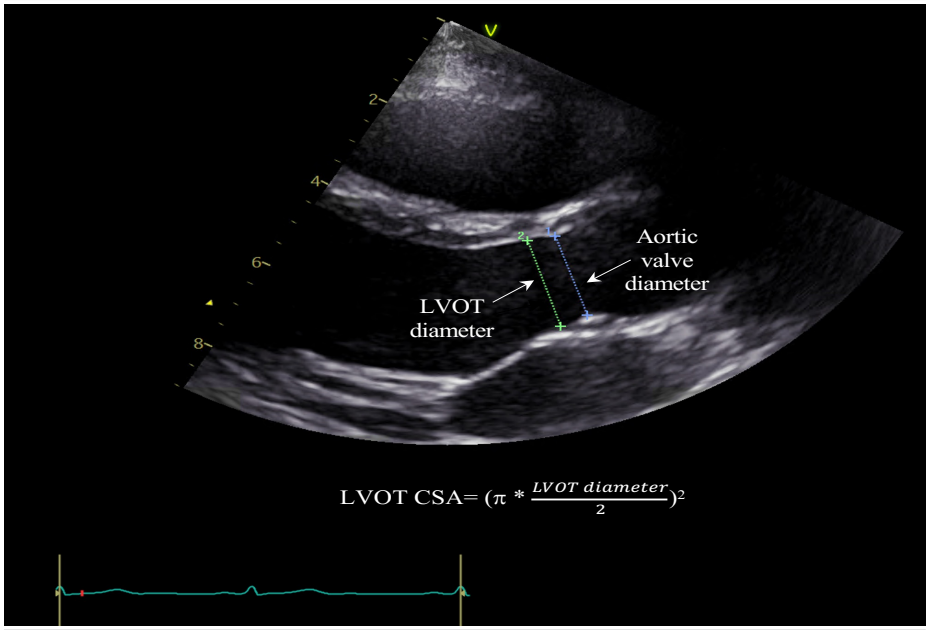
could recall the condition of some participants. In addition, some cardiac conditions (e.g. pacemaker, prosthetic valve) were recognizable by echocardiography making it difficult to be blinded for all patients. To limit personal bias, JLM revisited several of the exams with LKH to ensure proper measurement acquisition. In addition, she was the sole person to perform the analyses and transferred them to the database, limiting interpersonal variability. As well, severity class of the MHD was largely determined after the data collection was acquired with medical record (for mWHO category) and further echocardiography (for residual cardiac disease) review.

Dimensional Imaging: The following images were acquired as per guidelines of the American Society of Echocardiography [212]:

1. *Parasternal Long Axis (PSLX):* Parasternal long-axis images were acquired by placing the transducer adjacent to the sternum and obtaining an image along the long axis of the heart, that is from the base to the apex. Aortic valve and the left ventricular (LV) outflow tract were imaged for measurements of their diameters during LV end-systole for subsequent cardiac output (CO) calculation (Figure 2-1).
2. *Parasternal Short Axis (PSSX):* The transducer was placed adjacent to the sternum to acquire short axis images, that is, cross-sectional views of the heart with imaging 90 degrees clockwise from the parasternal long-axis image. 2D clips were acquired with 3-5 cardiac cycles at the LV base, mid-level, and apex, as done routinely. These images were obtained to assess the structural integrity and for later LV twist analyses.
3. *Apical Long Axis (APLX) 4- chamber:* A 4-chamber view with both atria and ventricles was obtained. This was achieved by placing the transducer on the left side of the chest at

the fifth intercostal space. 2D focused clips with views of all 4 chambers was done separately to evaluate structural integrity. Each clip was acquired for 3-5 consecutive beats. The 4-chamber view 2D clip was used to evaluate global longitudinal strain of the LV. In contrast to other measurements mentioned thus far which required only one frame of the clip, strain was acquired by assessing myocardial motion throughout the clip. In addition, the 4-chamber view of the LV was also used for LV volume determination through Simpson's biplane method which is explained later in this chapter.

Figure 2-1: Parasternal Long Axis View of the Aortic Valve and Left Ventricular Outflow Tract (LVOT)



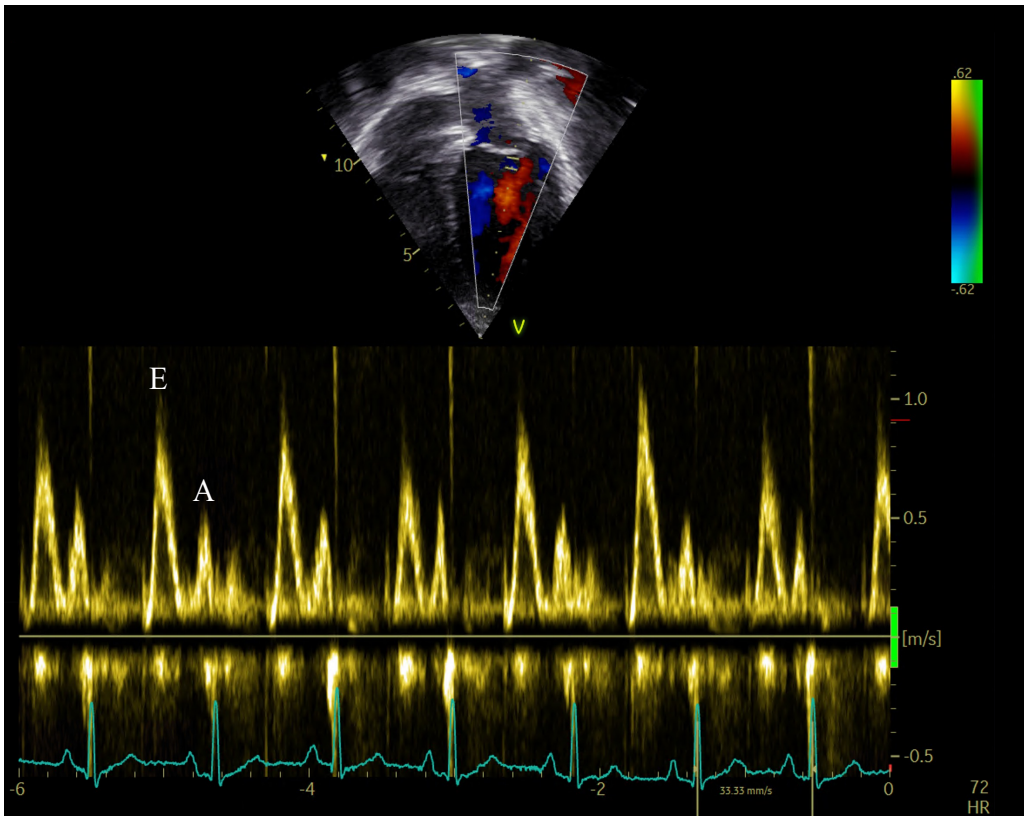
LVOT CSA: Left ventricular outflow tract cross-sectional area.

4. *Apical Long Axis (APLX) 2-chamber:* a 2-chamber view of the left atrium as well as the LV was obtained. A 2D clip with a focused view of the LV was particularly important for volume acquisition by Simpson's biplane method (Figure 2-5). The clip was acquired for

at least five consecutive beats. Visibility of the endocardium and epicardium was important during 2-chamber view acquisition for accurate volume assessment.

Color Doppler Flow Mapping: Color Doppler flow mapping was used to assess for mitral and tricuspid as well as aortic regurgitation and any valvular obstruction as well as to guide pulse Doppler interrogation.

Figure 2-2: Mitral Valve Pulse Wave Doppler Flow Patterns

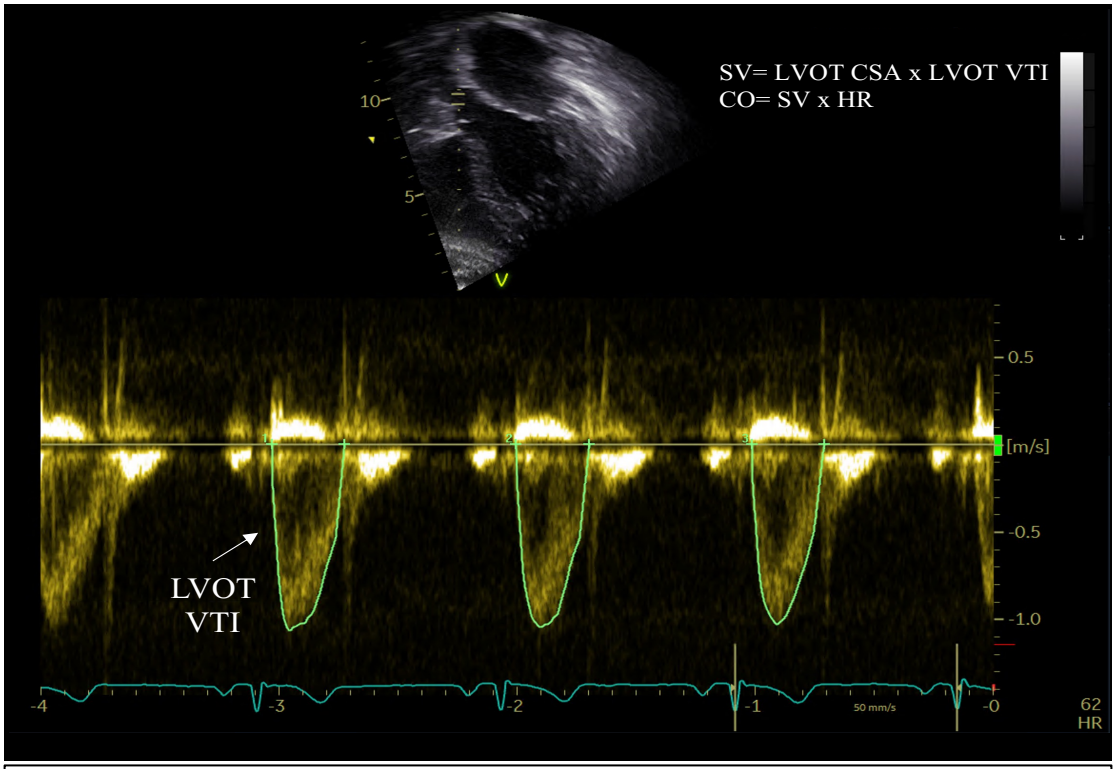


E: early diastole; A: atrial contraction.

Pulse wave Doppler: For mitral and tricuspid valve inflow Doppler, the sample volume was placed just below the valve annulus. E and A wave peak Doppler velocities were acquired for LV diastolic function assessment (Figure 2-2). Pulse wave Doppler profiles at the level of the LV outflow tract (LVOT) was then also acquired for assessment of the CO and stroke volume (SV) which require

velocity time integrals of the Doppler profile and heart rate (Figure 2-3). Pulse wave Doppler acquisition was done for at least 3-5 consecutive beats or cardiac cycles and measures were averaged.

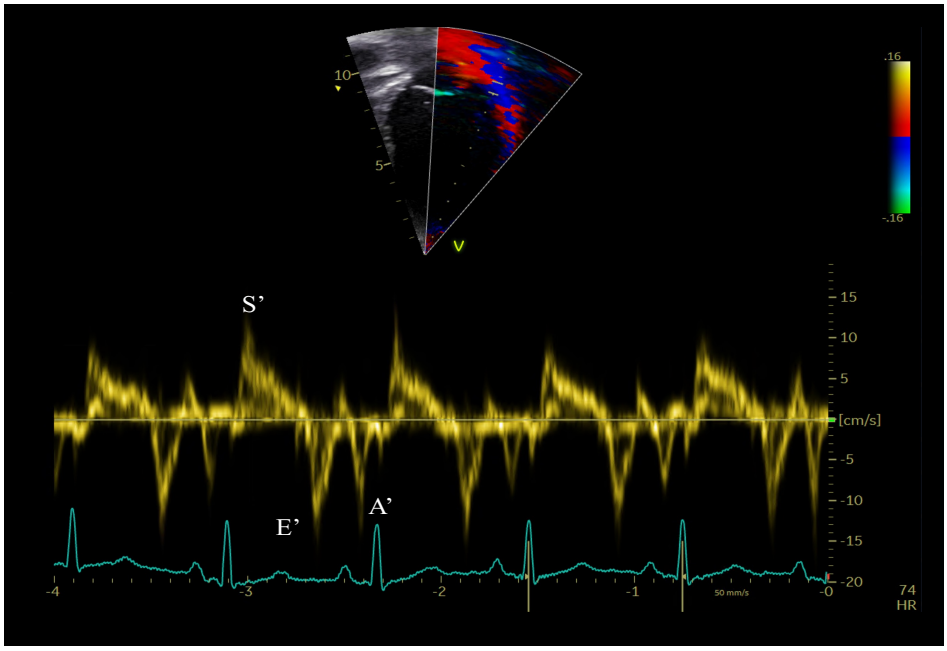
Figure 2-3: Left Ventricular Outflow Tract (LVOT) Pulse Wave Doppler Flow Patterns



LVOT VTI: left ventricular outflow tract velocity time integral; SV: stroke volume; LVOT CSA: left ventricular outflow tract cross-sectional area; CO: cardiac output; HR: heart rate.

Color Tissue Doppler: Color tissue Doppler imaging (TDI) at the level of the LV septal and lateral walls was also performed to assess annular tissue velocities (E', A' and S') for diastolic function assessment (Figure 2-4). This was achieved by selecting the TDI mode on the Vivid IQ which allows for the measurement of myocardial velocity at the site of cursor placement. TDI acquisition was performed for 3-5 consecutive beats.

Figure 2-4: Lateral Tissue Doppler Imaging (TDI)



S' represents systole, E' represents relaxation in early diastole and A' represents the atrial contraction in late diastole.

Simpson's Biplane Method

The Simpson's biplane method was used to determine the end-systolic volume (ESV) and end-diastolic volume (EDV) of the LV which in turn allows for a more reliable measurement of the LV ejection fraction (LVEF) as follows [213]:

$$\textbf{LVEF}= \frac{EDV-ESV}{EDV} \times 100$$

Normal values for LVEF range between 50-70% [214]. The Simpson's biplane method was specifically evolved based on the geometry and anatomy of the LV. It follows the principle that the addition of disks of equal height in the apical four-chamber and apical two-chamber views can provide an estimate of LV volumes at a given time during the cardiac cycle. These disks are

distributed along a perpendicular axis starting at the apex of the heart and ending at the base [215]. The following formulas were used for the calculation of LV volumes through Simpson's biplane method [216].

$$\textbf{Volume}_{\textbf{(individual disk)}} = \frac{p(axb)L}{4n}$$

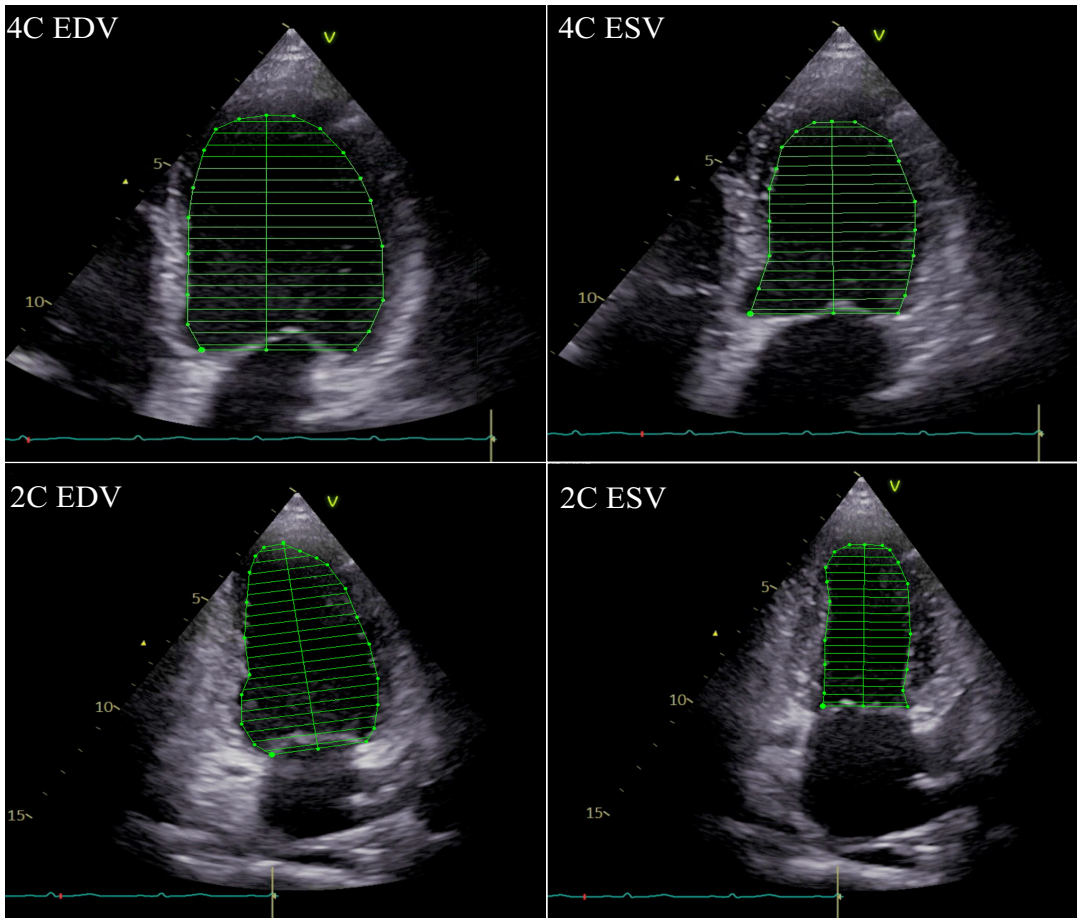
Where a and b are the vertical and horizontal diameters of the individual disk, L is the length of the LV cavity and n=20

$$\textbf{Volume total} = \frac{pL}{4n}\sum_{i=1}^{n} a_i \times b_i$$

Where $a_i \; and \; b_i$ are representative of the apical 4 and 2-chamber views of the LV.

While routinely applied in clinical practice, there are some limitations to this approach. For instance, when image acquisition is foreshortened, there can be an underestimation of volumes [215]. Also, although Simpson's biplane method is unique for LV anatomy, this can sometimes be limited when there are structural differences among patients [215, 217, 218]. Due to these limitations, we chose to use Simpson's volume acquisition for LVEF alone and SV was obtained with the LVOT velocity time integral (VTI) and the LVOT cross-sectional area [219]. This was achieved by tracing the area under the curve of the flow pattern obtained from the pulse wave Doppler at the level of the LVOT (Figure 2-3).

Figure 2-5- Simpson's Biplane Method in 4-Chamber (4C) and 2-Chamber (2C) Views



a & b: vertical and horizontal diameters of the individual disk; L: length of the LV cavity; n=20. EDV: end-diastolic volume; ESV: end-systolic volume.

Therefore, and as mentioned previously in this chapter, the 4-chamber and 2-chamber views of the LV were used for volume acquisition following Simpson's biplane method. This was achieved by selecting specific frames in the 2D clips corresponding to end-diastolic and end-systolic volumes and tracing of the LV cavity (Figure 2-5). For the end-diastolic volume, the frame before mitral valve closing was selected for manual tracing of the LV. The software (IntelliSpace) would then integrate disks in the LV. For the end-systolic volume, the frame before mitral valve

opening was selected for manual tracing of the LV. Each volume measurement was performed three times per view and then averaged.

Determination of Ventricular-Arterial Coupling (VAC)

We used the gold-standard for assessment of VAC, that is the single-beat estimate developed by Chen et al [196]. Although there is a simplified approach to quantifying VAC which incorporates the end-systolic pressure (ESP), SV and ESV that has been used in a previous study investigating VAC in pregnancy [30, 197], the single-beat method integrates the time-varying elastance of the LV in the equation and provides a more intricate evaluation of LV efficiency (Figure 2-5). This latter method had been used previously to assess VAC in post-Fontan adults [199], demonstrating clear differences relative to healthy individuals, which provided a better understanding of its utility in structural CHD in particular. VAC is determined by the ratio of arterial elastance (Ea), also known as the arterial load and the end-systolic elastance (Ees) or LV efficiency/function. The single-beat method includes the LVEF (acquired through Simpson's biplane method), the non-invasive estimated normalized ventricular elastance at onset of ejection (End(est)), the group-averaged normalized ventricular elastance at onset of ejection (End(avg)) and the ratio of the pre-ejection period to total systolic period (tNd). A normal VAC value is <1 [30].

Simplified VAC calculation

$$VAC = Ea/Ees$$

where $Ea = ESP/SV$, $Ees = ESP/ESV$

Single-beat estimate of VAC

$$VAC=Ea/Ees$$

$$where\ Es= ESP/SV$$

$$Ees= (DBP - (End(est)\times SBP \times 0.9))/End(est)\times SV$$

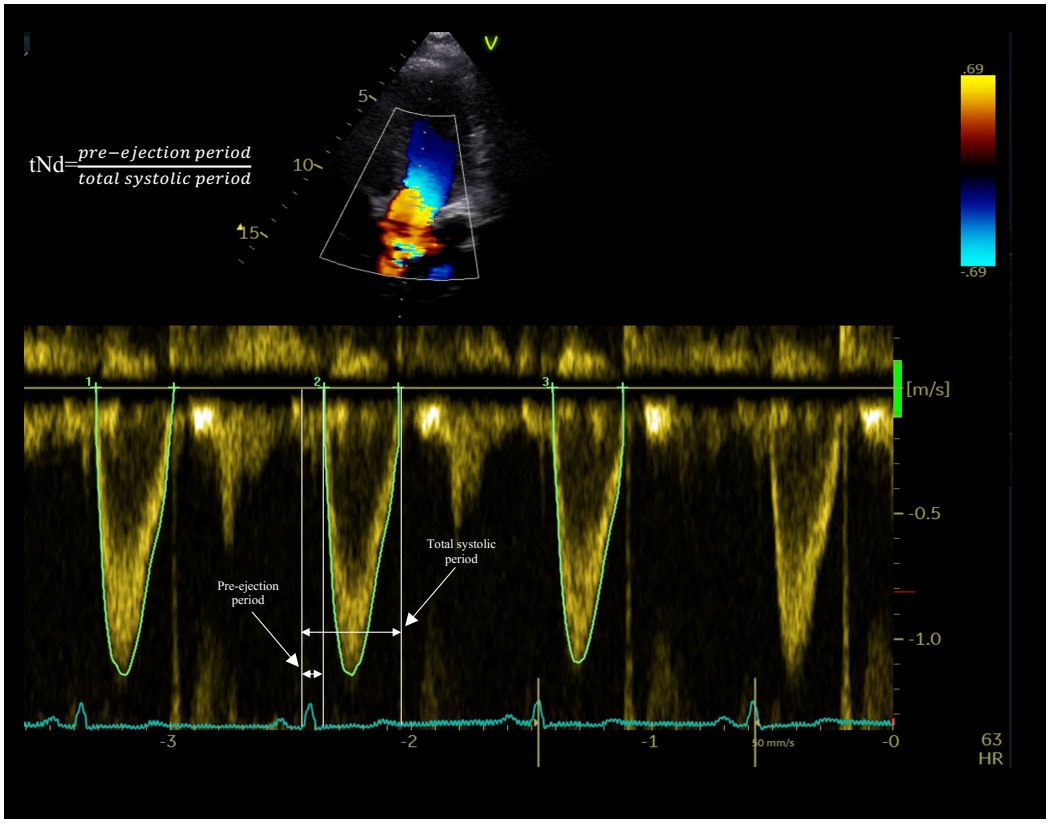
$$End(est)= 0.0275 - 0.165 \times LVEF + 0.3656 \times (DBP/SBP \times 0.9) + 0.515 \times End(avg)$$

$$End(avg)= 0.35695 - 7.2266 \times tNd + 74.249 \times tNd^2 - 307.39 \times tNd^3 + 684.54 \times tNd^4 - 856.92 \times tNd^5 + 571.95 \times tNd^6 - 159.1 \times tNd^7$$

$$tNd=\frac{pre-ejection\ period}{total\ systolic\ period}$$

The SV was obtained as previously mentioned. The tNd was acquired at the same time of LVOT VTI measurement. The pre-ejection period corresponded to the start of the QRS complex in the ECG signal to the start of systolic ejection. The total systolic period was determined as the start of the QRS complex until the end of systolic ejection (Figure 2-6).

Figure 2-6: tNd Acquisition for VAC Calculation



Indexing of Measures of Interest

Normally cardiac outcomes pertaining to volumes are indexed by dividing them by the BSA to improve prognostic performance and to allow for standardization of measures among individuals [220]. These measures include SV, ESV, EDV and CO. Although Ea and Ees include SV in their calculations, as they are used in the calculation for VAC, SV will be a common factor in both the numerator and denominator and will therefore be cancelled making indexing of SV by BSA unnecessary for the VAC calculation. Therefore, we primarily considered differences of the absolute values (not indexed) for Ea and Ees between groups (i.e. control vs MHD) in our analysis, however, indexed Ea and Ees were also acquired. Other measures of cardiac function were also

considered as absolute and indexed values; however, there was a particular focus on differences of indexed values between groups.

Cardiac Function Measures

Among the primary outcomes of this study were measures of systolic and diastolic function. Primary systolic function measures included CO (absolute and indexed), global longitudinal strain, strain rate and myocardial acceleration slope. Primary diastolic measures included EDV (indexed and absolute), E, E', E/A and E/E'. Secondary systolic outcomes included SV (absolute and indexed), ESV (absolute and indexed) and LVEF.

Systolic Function

Cardiac output: As shown previously in Figure 2-4 the CO was obtained by multiplying the SV obtained through the LVOT VTI and the heart rate (HR) [33, 35].

SV= LVOT CSA x LVOT VTI

CO= SV x HR

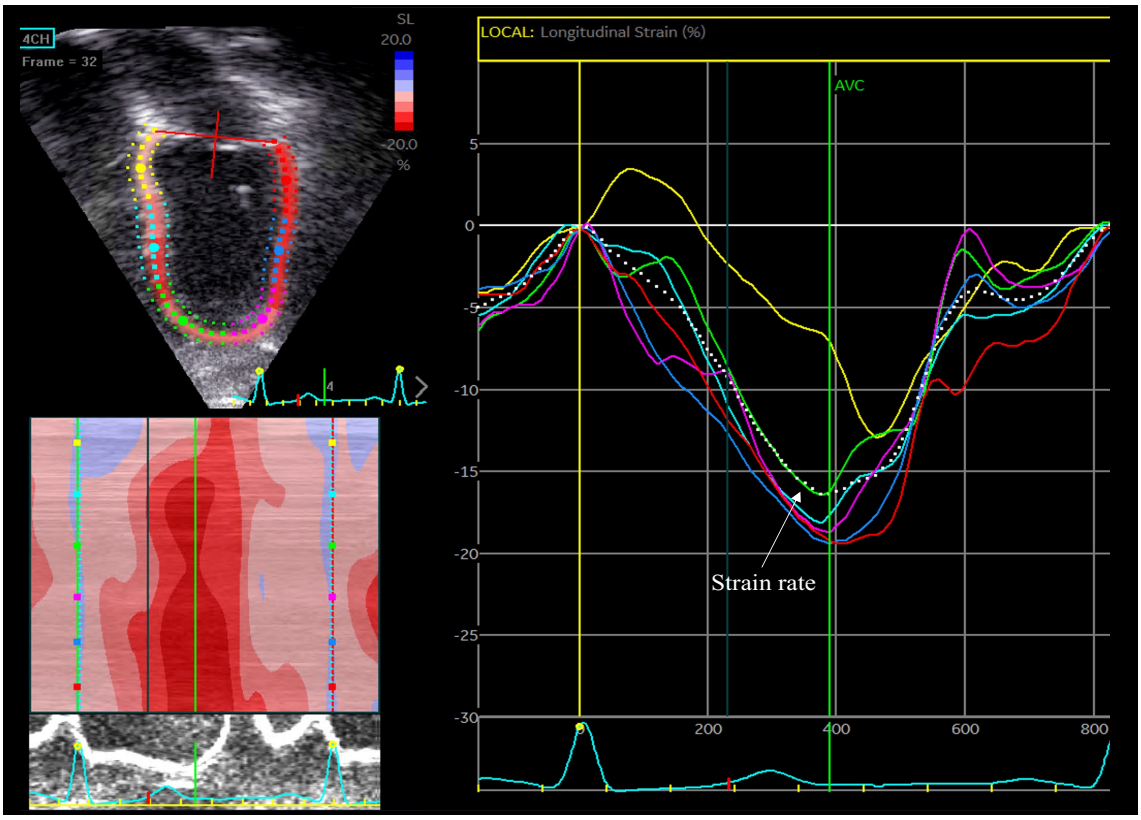
Global Longitudinal Strain (%) and Strain Rate: Strain is a measure used to assess myocardial function as it quantifies myocardial deformation of the LV in systole and in diastole. It represents the change in length of heart muscle fibers which explains the negative value for this parameter in systole and positive in diastole [49]. Given that it aims to evaluate the dynamics of heart muscle fibers, it assesses the intrinsic contractile properties of the myocardium, therefore it is

considered a less-load dependent assessment of myocardial contractility [48]. A negative global longitudinal strain of more than -16% is abnormal [221], that is, a less negative percentage (e.g. -10%) for global longitudinal strain is abnormal. The measurement of this parameter is achieved through speckle tracking echocardiography obtained from a 2D apical 4-chamber view with ViewPoint 6 and EchoPAC Suite (GE Healthcare).

Manual tracing of a 4-chamber view of the LV was performed. The software (ViewPoint 6 and EchoPAC Suite) then breaks down the tracing into six different sections to track them individually. This includes the septum at the level of the base, mid-level and apex of the heart. The same is done for the lateral wall of the LV [222]. Following the tracking of the different sections, the software displays curves tracking the strain of specific segments and provides a dotted line for the global longitudinal strain (Figure 2-7).

Optimal images consisted of clear resolution of the ventricular walls and capturing of several cardiac cycles ranging from 40-80 frames per second during the time of image acquisition [223]. As per current guidelines, when more than two of the required segments of the ventricle for strain quantification were suboptimal, or when the frame rate was lower than 40, strain measurements were not performed [224]. This is done given that a low frame rate acquisition could affect tracking ability of structures as well as edge definition of the LV [225]. The rate at which myocardial deformation occurs is the strain rate [49]. The strain rate was measured at the lowest point of the dotted curve before aortic valve closure, which provides a value for the strain rate during systole [226] (Figure 2-7).

Figure 2-7- Acquisition of Global Longitudinal Strain (GLS%) of the Left Ventricle Through Speckle Tracking Echocardiography

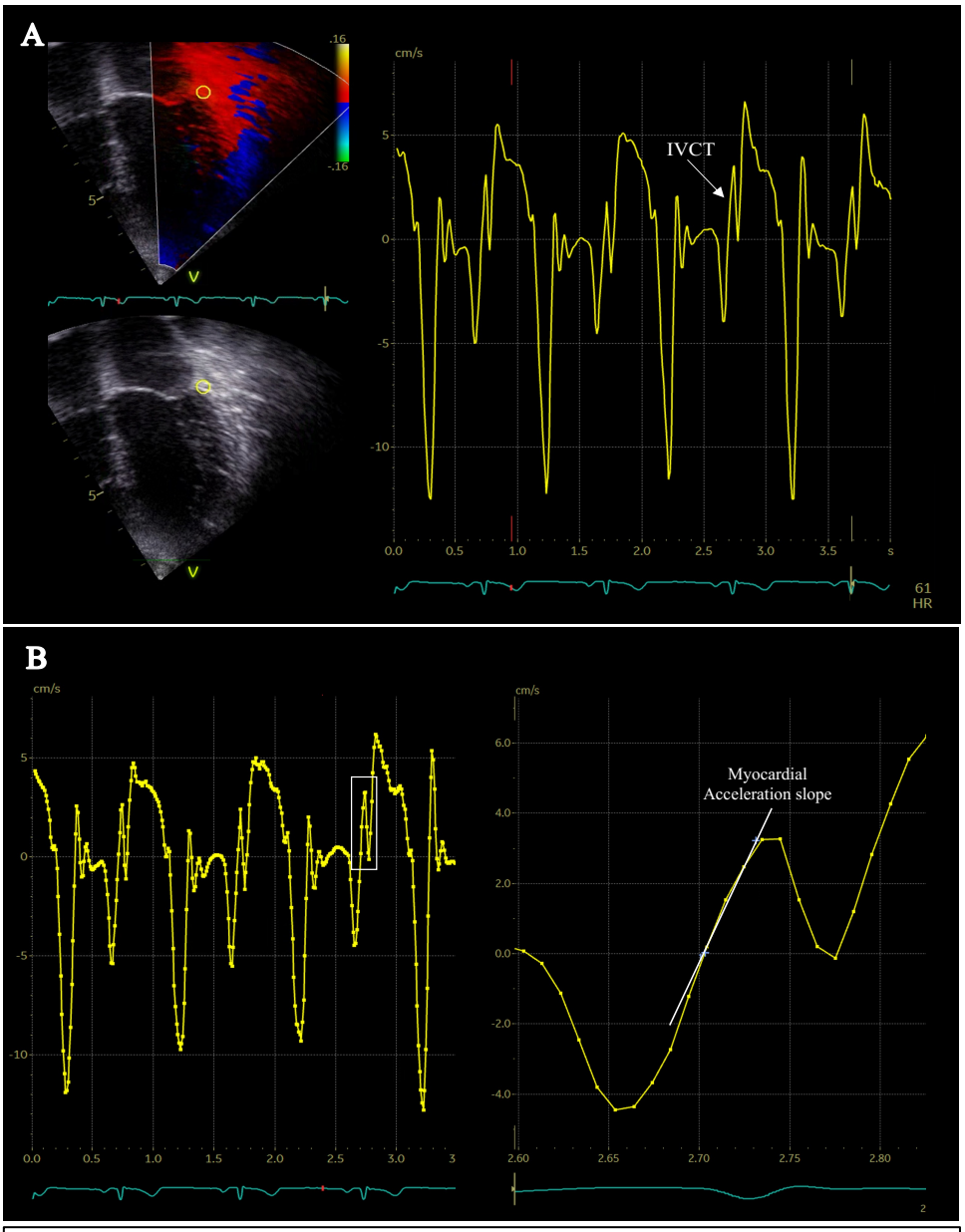


AVC: aortic valve closure.

Myocardial Acceleration Slope: Another less load-dependent measure of systolic function that was assessed was myocardial acceleration. This is achieved by measuring the slope of myocardial acceleration. The myocardial acceleration slope was obtained from a 4-chamber 2D clip of the LV with the TDI function. More specifically, it was acquired by measuring the slope of the isovolumic contraction (IVCT) given that this period is where the LV contracts without a change in volume to prepare for systole. Some argue that this phase of the cardiac cycle, or more particularly, the slope during this phase of the cardiac cycles correlates with measures of LV contractility, making it a less-load dependent measure of contractility [227, 228]. The slope was

measured with at least three data points above zero. Three consecutive slope measurements were averaged for analysis (Figure 2-8).

Figure 2-8- Tissue Doppler Imaging (TDI)



A. Lateral wall TDI. B. Myocardial Acceleration slope. IVCT: isovolumic contraction.

Diastolic Function

Diastolic function parameters measured included pulsed Doppler interrogation of ventricular inflows to assess E (early diastole) and A (atrial contraction) wave velocities and their ratios, and respective tissue Doppler E' and A' mitral annular velocities and their ratios. E/E' from both pulsed and tissue Doppler velocities were also used to examine diastolic function [229]. For both flow and tissue velocities, three measurements for each parameter were made with the help of a caliper and were then averaged.

E/E' has been previously shown to correlate with LV end-diastolic pressure [210, 230-232]. This measure follows the principle that after systole, the LV untwists and relaxes creating a pressure gradient between the left atrium to the LV which promotes a rapid, passive filling or early diastole (E wave) [233]. However, when there is impaired relaxation of the LV, there can be increased pressure required to fill the LV which is reflected by a decrease in E and decreasing E/A ratio. Normally, the velocity of E, exceeds that of A, flow from atrial contraction, resulting in a E/A>1 [232]. In addition, E' represents myocardial relaxation during early diastole and it decreases with impaired LV relaxation [229]. Therefore, the study of E/E' can provide information about LV dynamics during diastole. Normally, E/E'<8 is normal and E/E'>15 is indicatory of increased LV filling pressures [234-236].

In addition to these measures of diastolic function, EDV was also compared among groups. As mentioned previously, EDVs were acquired through Simpson's biplane method.

Fetal Echocardiography

Fetal echocardiograms were performed for all participants with fetal ultrasound equipment (ACUSON Sequoia, SIEMENS Healthineers, GE Healthcare Voluson System). The transducer frequency ranged from 2-9 MHz which was within suggested guidelines [237]. Various transducers were used depending on the equipment available at the time of the visit. For instance, the curved 9C3 transducer was used with the ACUSON Sequoia ultrasound machine, and the curved RM6C transducer was used with the Voluson ultrasound machine and the curved 7CF2 transducer was used with the SIEMENS ultrasound machine. The exam was performed by a trained sonographer, medical fellow or echocardiologist depending on staff availability. These studies were performed based on current published guidelines by the American Society of Echocardiography (ASE) [237, 238].

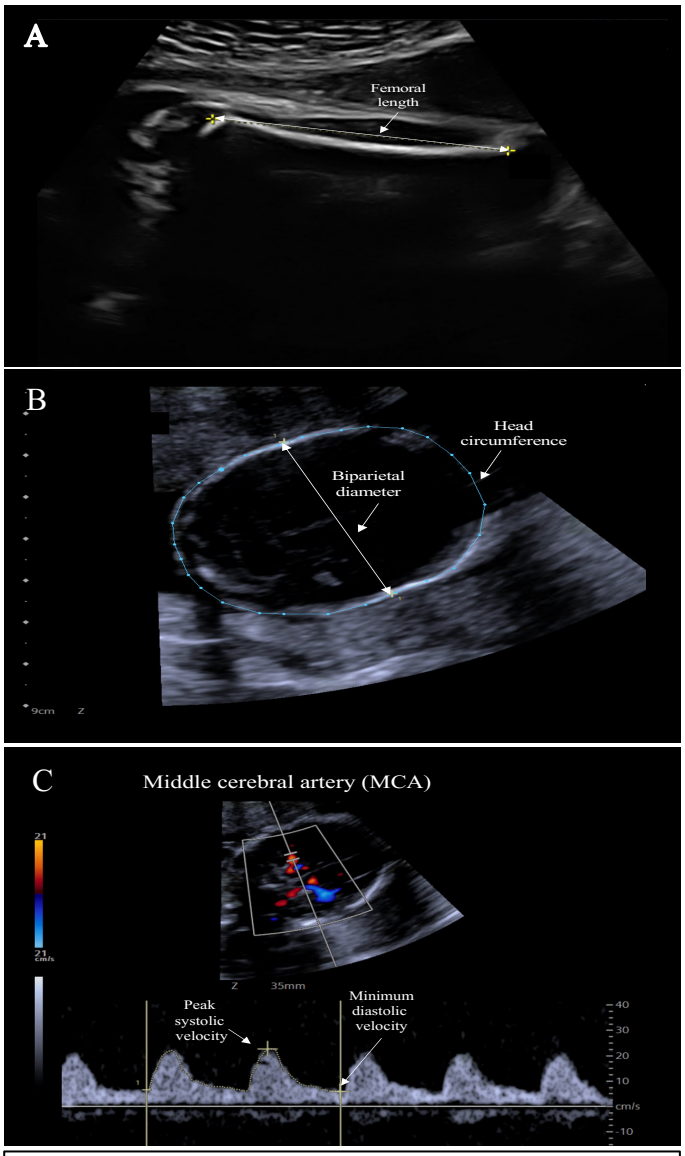
These studies included a detailed assessment of the fetal heart structure and function, assessment of fetal heart rate and rhythm, assessment of the umbilical arterial and venous flow, middle cerebral artery Doppler profiles and fetal biometry [239].

Fetal Heart Structure

Fetal heart structure assessment consisted of identification of all important structures including atria, ventricles, valves, and vessels. However, this information was not used for data analysis. The structural integrity and function of the fetal heart was simply assessed by the cardiologist in clinic to determine whether fetal pathology was presented and whether the patient could be included in the study. Fetal heart rate was obtained during the exam and used for subsequent data analysis.

Fetal Biometry and Middle Cerebral Artery

Figure 2-9- Fetal Biometry and Middle Cerebral Artery (MCA)



A. femoral length. B. biparietal diameter and head circumference. C: Middle cerebral artery (MCA).

Measures of fetal growth including femoral length and head circumference [240] were obtained with a caliper function. The femoral length was determined as the length between the beginning of the femur to the end (Figure 2-9.A). The head circumference was acquired by manually tracing the outline of the fetal head (Figure 2-9.B). Each measurement was performed once. Although the biparietal diameter was also measured, it was not included in the data analysis.

Routinely, middle cerebral artery Doppler waveforms including the pulsatility index (PI) were also acquired to assess fetal health. In particular, this measure evaluates blood flow profiles in the fetal brain. Therefore, using the pulse wave cursor, the blood flow profile of the middle cerebral artery was measured for at least 3-5 consecutive beats. Tracings of the Doppler flow patterns were performed to obtain the peak

systolic velocity, minimum diastolic velocity and time-averaged velocity [241] either during the exam by the individual performing the echocardiogram or after as part of the offline analyses (Figure 2-9.C). Values for the different velocities were performed for at least two consecutive cycles and were then averaged.

DICOM images were stored on IntelliSpace Cardiovascular (ISCV) (Phillips) for subsequent offline analyses. Following measurements, we obtained both centiles and z-scores to describe the distribution of fetal biometry measures and middle cerebral artery PI among participants with clinically certified calculators for fetal biometry [242, 243]. This was achieved by inputting the gestational age and respective value (e.g. length in mm or PI) in the calculator.

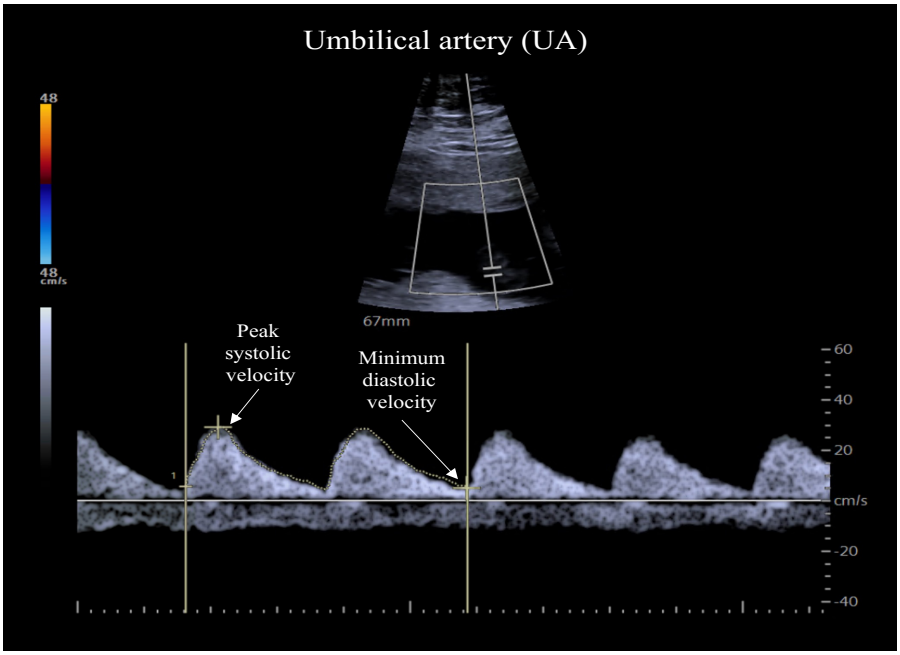
Assessment of the Uteroplacental-Fetal Circulation

As with other measures of fetal health, the transducer used depended on the equipment available during the time of the visit (i.e. ACUSON Sequoia, SIEMENS Healthineers or GE Healthcare Voluson System). Doppler flow patterns were acquired and recorded at the level of the umbilical artery (UA) and both uterine arteries (UtA) (Figures 2-10 &2-11).

We chose to examine the UA and UtA Doppler flow profiles as both provide information about the health of the uteroplacental circulation and the level of perfusion. In fact, both measures have been used for the prediction of fetal growth outcomes [244]. Increased impedance to flow as depicted by an increased PI in either the UtA or UA can provide an indication of increased downstream resistance [134, 149, 245].

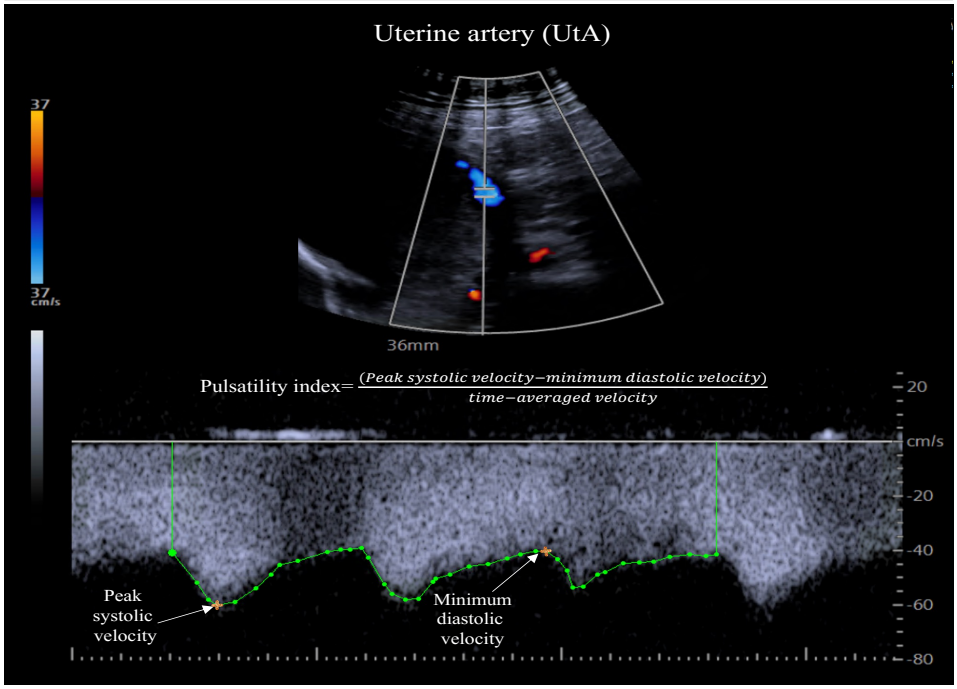
The measurement of the UA Doppler flow profile was achieved by placing the pulse wave cursor at the level of the umbilical cord away from the cord insertion into the fetus. As with the middle cerebral artery, tracings of the Doppler flow patterns were performed to obtain the needed variables for the calculation of the PI either during the exam by the individual performing the echocardiogram or after as part of the offline analyses (Figure 2-10). Values of at least two consecutive cycles were averaged.

Figure 2-10- Umbilical Artery (UA) Doppler Flow Patterns



The same procedure as described above was performed for the tracing of Doppler flow patterns for UtA PI measurements (Figure 2-11). Given that there are two uterine arteries, we attempted to obtain Doppler flow patterns for both uterine arteries resulting in a mean UtA PI. In some cases, the right, left or both UtAs were not visible or clear. Therefore, three categories for UtA PIs were established, that is, right UtA alone, the left UtA alone or the mean UtA.

Figure 2-11- Uterine Artery (UtA) Doppler Flow Patterns



Visible are the peak systolic velocity and minimum diastolic velocity. The pulsatility index is calculated as the ratio of the difference between the peak systolic velocity and minimum diastolic velocity over the time-averaged velocity.

Normally, fetal and uteroplacental parameters are assessed in terms of z-scores and centiles. Clinically, it is accepted that the cut-off for concern in terms of UA and UtA PI are values >95th centile [147, 246, 247]. We attempted to obtain both centiles and z-scores to describe the distribution of Doppler parameters among the participants with clinically used calculators for Dopplers [242, 243]. To obtain z-scores and centiles, the gestational age and PI value were inputted which normally yielded a z-score and centile for a given value. However, although reference values have been available for UtA PI starting at 11 weeks of gestation and for fetal growth parameters starting 14 weeks of gestation, most normative data published for UA PI have started at 20 weeks. Given that some participants had gestational ages starting at 18 weeks of gestation, centiles for UA were estimated from published reference values of a peer-reviewed source [248]. Therefore, it

was not possible to obtain z-scores for all the parameters of interest in every participant which would have provided a more standardized value for comparison among groups. Given that not all z-scores were available, centiles were used as the determining factor for comparison between MHD and control participants. As mentioned previously, normally PI values >95th centile are clinically relevant and normally analyses are performed by quantifying the proportion of individuals above that set value [147, 156, 244]. We chose to determine the number of participants with values >95th centile in addition to comparing the distribution of centiles among groups to determine whether a group had a tendency towards higher PIs.

Statistical Analysis

Statistical analyses were conducted using SAS System (Version 9.4, SAS Institute Inc, 2016) with the assistance of a statistician (JB). Graphs were created with GraphPad Prism (GraphPad Software Version 10.1.0, LLC, 2023). Initially, tests for normality were performed for demographic characteristics as well as every outcome to determine which test was appropriate for comparison between MHD and control participants. Given that the sample size was relatively small in each group (n<50), the Shapiro-Wilk test was used to assess normality where a P-value <0.05 indicated a non-normal distribution of data [249].

Independent Samples t-tests

Outcomes with a normal distribution were compared between groups with an independent samples t-test where a P-value <0.05 indicated a significant difference between groups. For demographic characteristics, age of participant when they became pregnant, the body surface area

(BSA), body mass index (BMI) and gestational age had normal distributions and were therefore compared with an independent samples t-test. Baseline cardiac parameters including heart rate, systolic, diastolic, and mean arterial pressure also presented a normal distribution. The outcomes of interest with a normal distribution included VAC, absolute, absolute and indexed Ees, CO indexed, global longitudinal strain, strain rate, myocardial acceleration slope, the absolute and indexed values for end-diastolic volume, E from mitral valve inflow measurements and E'. Other cardiac outcomes included the absolute SV, indexed SV and LVEF. In this case, data was presented as mean and standard deviation.

Mann Whitney U Test

When data did not present a normal distribution, a non-parametric test was required. In this case, a Mann Whitney U test was used for values or outcomes that were non-parametric. Significant differences among groups were defined as a P-value <0.05. Data were presented as median and interquartile range [IQR]. Gravidity, parity, and the number of pregnancy losses were compared with the latter test as they presented a non-normal distribution. However, these last three variables were presented as a median and range given the nature of the data. The comparison of NT-proBNP between groups was also performed with a Mann Whitney U test.

Cardiac outcomes that were compared with a Mann Whitney U test included the indexed Ea, absolute value for CO, E/A and E/E'. Other outcomes included the absolute and indexed end-systolic volumes. In addition, fetal and uteroplacental outcomes compared with the same test included the head circumference, femoral length, fetal heart rate and middle cerebral artery PI. The right left and mean UtA PI, as well as the UA PI were also treated as non-parametric data.

Medication Use and Comorbidities

Given that some participants indicated the use of medications and had concurrent health conditions, an analysis was performed to determine whether there was a difference among groups in these variables. A Fisher's exact test was performed to compare medication use and the presence of comorbidities among groups. Significance was defined as a P-value <0.05.

Regression Analyses

We wanted to investigate whether there was an association between various outcomes of interest and VAC, therefore we used a multilinear regression analysis. This analysis did not include variables that were already included in the equation used to calculate VAC or values that presented collinearity. Therefore, in a multiple regression model, we explored the association between global longitudinal strain and E/E' with VAC. Strain rate and the myocardial acceleration slope were not included in this model given that they are related to global longitudinal strain. This association was presented as an adjusted R^2 and standardized B coefficient where R^2 is a measure of the ability of the whole model to predict a change in VAC. High predictability was defined as an adjusted $R^2 > 0.7$. The standardized B coefficient represents the effect of a given variable (independent variable) on VAC (dependent variable); it was accompanied by a P-value where significance was defined as $P<0.05$.

Importantly, we included any demographic characteristics that were significantly different between MHD and control participants in the regression model to explore how that given variable might affect VAC, our primary outcome of interest. However, in the case of collinearity among these variables, only one variable was chosen to be included in the analysis.

Individual linear regression analyses were also performed to see the effect of VAC on various outcomes of interest where a high predictability ability was defined as an adjusted R^2 >0.7. The standardized B coefficient represented the effect size of VAC (independent variable) on the given measure (dependent variable) and significance was defined as P<0.05.These analyses were performed to evaluate the predictive ability of VAC of NT-proBNP, the right, left, mean UtA PI and UA PI. Therefore, individual linear regression analyses were performed where a high predictability ability was defined as an adjusted R^2 >0.7. The standardized B coefficient represented the effect size of VAC (independent variable) on the given measure (dependent variable) and significance was defined as P<0.05.

Analysis of Variance (ANOVA) for Subgroup Analyses

Given that we created two subgroups for MHD severity (mild and moderate-severe) in the MHD group, we used a one-way ANOVA with a Bonferroni correction for parametric data. The outcomes compared between groups with this test included VAC, absolute and indexed Ea, absolute and indexed Ees, indexed CO, global longitudinal strain, strain rate, myocardial acceleration slope, indexed SV, LVEF and indexed end-diastolic volume and E'. Significance was defined as P<0.05.

Kruskal-Wallis Test for Subgroup Analyses

Subgroup analyses for non-parametric data were performed with a Kruskal-Wallis test where significance was defined as P<0.05. The cardiac outcomes compared between groups with

this test included the indexed end-systolic volume and E/E'. Uteroplacental and fetal outcomes analyzed with this test included the right, left and mean UtA PI, as well as the UA PI. The head circumference, femoral length, fetal heart rate and middle cerebral artery PI were also included.

Analysis of Covariance

Following the evaluation of medication use among groups, we decided to perform an analysis of covariance (in addition to MHD) if the use of a given medication was significantly different among groups. In this case, a linear mixed model was performed to assess the effect of a given medication on various outcomes including VAC, absolute and indexed Ea, absolute and indexed Ees, indexed CO, global longitudinal strain, indexed end-systolic volume, LVEF, indexed end-diastolic volume and E/E'. A significant effect was defined as a P-value <0.05.

The same procedure was followed for uteroplacental outcomes including the right, left and mean UtA PI, as well as the UA PI. Head circumference, femoral length, fetal heart rate and middle cerebral artery were also included in the analysis.

Post-Hoc Power Analysis for VAC

Given that there is no existing literature examining VAC in MHD compared to control pregnancies, a post-hoc power analysis was performed to determine if the sample size for our main outcome of interest was large enough to show significant differences among groups. The type of statistical test used was a t test with a post-hoc power calculation. This was achieved by using G power, a validated software [250], where information including group mean value, standard deviation

and sample size yielded the power of the outcome of interest, where power (1- ß error probability) ≥ 0.80 shows a significantly powered study.

CHAPTER 3: RESULTS

Participants Recruited

From June 2021 through October 2023, 77 pregnant participants were recruited into the study; however, as a consequence of not meeting inclusion criteria or attrition (see below), our study only included 33 clinical maternal heart disease (MHD) patients and 32 controls. Table 3-1 summarizes the demographics and pregnancy histories of the participants.

Table 3-1: Participant Demographics and Pregnancy Histories

	Control	**MHD**	
Number of participants	32	33	
Number of deliveries to date	31	31	
	Control	**MHD**	**P-value**
Maternal age	31.6±2.8	30.6±4.6	0.38
BSA at visit (m^2)	1.8±0.20	1.9±0.20	0.071
Pre-pregnancy BMI (Kg/m^2)	25.2±4.1	25.5±4.0	0.85
Gestational age	21.5±1.6	20.0±1.2	**0.0001**
Gravidity	2 [1-5]	2 [1-5]	**0.0089**
Parity	0 [0-2]	1 [0-2]	**0.041**
Pregnancy losses	0 [0-3]	1 [0-4]	**0.038**
Number with history of preeclampsia	1	2	1.00

BSA: body surface area; BMI: body mass index. All values are presented as mean and standard deviation, except for parity, gravidity and losses given that they have a non-parametric distribution. Therefore, they are presented as median [range].

Two control participants withdrew due to time constraints and nine were disqualified. Of the latter 9, 4 had miscarriages, including 3 clinical and 1 control participants, 1 clinical participant was lost to follow-up, 1 control was found to have a high-risk pregnancy due to gestational hypertension, 1 control had scheduling problems due to COVID-19, 1 potential clinical participant ultimately did not meet the cardiac criteria (tachycardia induced cardiomyopathy) and 1 other control was found to have fetal cardiac pathology and was disqualified (i.e. excluded). One clinical

participant did not have stored data in the software used for analysis (lost data) for the midtrimester visit, resulting in a total of 65 participants (33 clinical and 32 control) included in the final analyses.

Clinical Participants

The age for the 33 MHD participants ranged from 19-43 years. Of these clinical participants, 29 (88%) had congenital heart disease (CHD), 10 (34%) of whom had mild and 19 (66%) had moderate-severe MHD (Table 3-2). In addition, 23 of the 29 (79%) were post intervention. Four of the 33 (12%) MHD participants had acquired heart disease (AHD), including 2 with mild and 2 with moderate-severe MHD. Therefore, a total of 12 participants were considered to have mild MHD and 21 moderate-severe MHD according to our categorization based on the modified World Health Organization classification (mWHO) [19-21]. The structural and hemodynamic severity of all participants is summarized in Table 3-2. Based on the mWHO, nine (27%) of the MHD participants were in mWHO category I, considered to have no significant maternal or pregnancy risk, nine (27%) were in category II with a small increased risk, 14 (42%) were in category II-III with a moderate increases risk and one (3%) was considered to be in category III with a significantly increased risk in maternal mortality or morbidity. None of the cohort participants were considered to be a category IV with substantial maternal and pregnancy mortality and morbidity risks. With respect to New York Heart Association classification, all reported either no symptoms (class I, n= 23, 70%) or minor symptoms (class I-II or II, n= 10, 30%).

Table 3-2: Cardiac Profile, Severity and Risk Classification of MHD Participants						
Patient	**Cardiac Diagnosis**	**Interventions**	**Residual Disease**	**Severity When Residual Pathology if Considered**	**mWHO**	**NYHA**
1	ASD	None	Moderate TR, mild PR, severe RA, and RV dilation	Moderate-Severe	II	I-II
2	S/P coarctation	S/P surgical repair of coarctation (16 months)	None	Moderate-Severe	II-III	II
3	Hypertrophic CM	S/P AICD (23 years)	Severe LV hypertrophy	Moderate-Severe	II-III	I
4	VSD	S/P surgical repair (childhood)	None	Mild	I	I
5	ToF	S/P surgical repair (6 months), AICD (13yrs), surgical PVR (15yrs), TCPV (23yrs)	Mild PR, mild RV dilation and dysfunction	Moderate-Severe	II	I
6	Aortic valve stenosis and ASD	S/P Ross procedure and ASD (4yrs), S/P PVR (19yrs)	Moderate RV-PA conduit obstruction, no PR, mild TR, mildly dilated aortic root	Moderate-severe	II-III	II
7	Coarctation & BAV	S/P surgical repair coarctation (infancy)	Mild aortic dilation	Moderate-Severe	II-III	I
8	S/P ASD	S/P surgical repair (28yrs)	None	Mild	I	I
9	AS	S/P aortic valvuloplasty (32yrs)	Mild AS, moderate AR	Mild	II	I
10	RV CM	S/P AICD (25yrs)	Mild regional RV dysfunction	Mild	II-III	II

11	S/P ToF	S/P BT shunt (6 months), S/P repair (3yrs),	Moderate PS, moderate PR, mild AR	Moderate-Severe	II	I
12	BAV	None	Mild-moderate AR, no AS	Mild	II-III	I
13	AS and aortopathy	S/P Ross procedure (25yrs)	Mild-moderate AR, trivial PR	Moderate-Severe	II	II
14	Pulmonary valve stenosis	S/P balloon valvuloplasty (2yrs)	Moderate-severe PR with moderate RV dilation, mild PS	Moderate-Severe	I	I
15	BAV, subaortic stenosis	S/P aortic valvotomy (infancy), S/P AVR (7yrs), S/P AVR (26yrs)	Mild MR, mild MS, moderate AS, mild RV dilation	Moderate-Severe	II-III	I
16	PS	None	Mild PS and PR	Mild	I	I
17	AVSD	S/P AVSD (5 months), S/P subaortic stenosis resection (3yrs)	Moderate TR	Moderate-Severe	II-III	I
18	Dilated CM	None	Reduced LV systolic function (LVEF 45-50%)	Moderate-Severe	III	II
19	Hypertrophic CM	AICD 2019	Mild-moderate asymmetric septal hypertrophy, no AR or outflow obstruction	Mild	II-III	II

20	AS	None	Moderate AS (peak 56/mean 30mmHg)	Moderate-Severe	II-III	I
21	ToF	S/P surgical repair (6 months), S/P surgical PVR (12yrs)	Mild-moderate PR, mild PS, mild TR, no RV dilation	Moderate-Severe	II	II
22	ASD	S/P surgical repair (7yrs)	Trivial TR	Mild	I	I
23	Incomplete AVSD	S/P AVSD repair (16yrs)	Moderate MR	Moderate-Severe	II	I
24	ASD	None	Mild MR	Mild	I	I
25	S/P ASD	S/P device closure (27yrs)	None	Mild	I	II
26	S/P VSD	S/P surgical repair (5 months), postoperative AVB S/P pacemaker	Moderate-severe AR, moderate LV dilation and dysfunction (LVEF 40-45%), mild RV dysfunction	Moderate-Severe	II	I
27	Tricuspid valve dysplasia	None	Moderate to severe TR, moderate RV dilation	Moderate-Severe	II-III	I
28	Coarctation, BAV	S/P stent angioplasty (15yrs)	No AS, AR, 16mmHg arch gradient	Moderate-Severe	II-III	II
29	Small VSD	None	Small VSD	Mild	I	I
30	S/P ASD	S/P surgical repair (35yrs)	Normal function	Mild	I	I
31	AS, BAV	S/P AVR (27yrs)	Moderate AS, mild aortic root dilation	Moderate-Severe	II-III	I
32	ToF	S/P ToF (6 months), S/P	Mild PR, no RV outflow obstruction,	Moderate-Severe	II	I

		surgical PVR (19yrs)	mild RV dilation			
33	Ebstein's anomaly	S/P TVR (6yrs), S/P re-TVR (12yrs)	Moderate-severe TS (mean 12mmHg), mild TR, moderate-severe RV dilation and dysfunction	Moderate-Severe	II-III	I

S/P: status post; ASD: atrial septal defect; RA: right atrium; RV: right ventricle; TR: tricuspid regurgitation; PR: pulmonary regurgitation; LV: left ventricle; CM: cardiomyopathy; AICD: automatic implantable cardioverter defibrillator; VSD: ventricular septal defect; ToF: Tetralogy of Fallot; PVR: pulmonary valve replacement; TCPV: transcatheter pulmonary valve replacement. AS: aortic stenosis; PA: pulmonary artery; BAV: bicuspid aortic valve; AVR: aortic valve replacement; AoV: aortic valve; AR: aortic regurgitation; PS: pulmonary stenosis; LVEF: left ventricular ejection fraction; PV: pulmonary valve; MR: mitral regurgitation; MS: mitral stenosis; AVSD: atrioventricular septal defect; AVB: atrioventricular block; TS: tricuspid stenosis.

The mean gestational age at the time of the assessments included in this investigation for the MHD participants was 20.0±1.2 weeks. Thirteen (39%) of the 33 were nulliparous and the majority of the others (17, 62%) had had a single previous child. Eleven (33%) had a previous history of spontaneous abortion, and three had therapeutic abortions. Of those who had spontaneous abortions, two reported their occurrence at <16 weeks of gestation. Two individuals had a history of preeclampsia in previous pregnancies. The group had a mean pre-pregnancy body mass index (BMI) of 25.5±4.0 Kg/m^2 and a body surface area (BSA) at the time of the study of 1.9±0.20 m^2.

With respect to other health issues, one had polycystic ovarian syndrome, two had type II diabetes and one presented with triple X syndrome. Also, 17 (52%) of those in the MHD group were on medications during the pregnancy including 7 (21%) with a beta-blocker, 3 (9%) on

levothyroxine, 4 (12%) on anti-depressants or anxiety medication, 2 (6%) on insulin, 2 (6%) on warfarin and 1 on anti-seizure medication.

Control Participants

The age for control participants ranged from 27-39 years. The mean gestational age was 21.5±1.6 weeks. The majority (20, 63%) of these women had had been nulliparous, whereas only 12 (38%) had at least 1 previous live birth when recruited into the study. Three (9%) had spontaneous abortions and 5 (16%) had a history of elective abortions. One individual had a history of preeclampsia in a previous pregnancy. The group had a mean pre-pregnancy BMI of 25.2±4.1 Kg/m^2 and a BSA at the time of the study of 1.8±0.20 m^2. Three (9%) had a diagnosis of hypothyroidism confirmed with clinical testing and were on levothyroxine with normal thyroid tests in the midtrimester. Six others were on levothyroxine for borderline low thyroid levels. One had a diagnosis of polycystic ovarian syndrome. One individual indicated the use of anti-anxiety medication, and one participant had a prescription for warfarin for a previous pulmonary embolism.

Demographic, Pregnancy & Health History and Medication Use Comparisons

Maternal age, BSA at time of the assessment and pre-pregnancy BMI were not different between MHD and control groups. In general, MHD individuals had significantly higher gravidity P=0.0089), higher parity (P=0.041) and losses (P=0.038) than control individuals. Gestational age was significantly lower (P=0.0001) in MHD participants than control participants (Table 3-1). Therefore, MHD and control participants were only matched by maternal age, BSA and pre-pregnancy BMI.

Comorbidities and use of various medications, summarized in Table 3-3, were compared between groups to control for confounding variables. Clinical patients had a significantly increased use of beta-blockers compared to controls (P=0.011) (Table 3-3).

Table 3-3: Medication Use and Comorbidities in Control and MHD Participants

Medication	**Control (n)**	**MHD (n)**	**P-Value**
Beta-blocker	0	7	**0.011**
Levothyroxine	9	3	0.061
Anti-depressants/anxiety	1	4	0.35
Insulin	0	2	0.49
Warfarin	1	2	1.00
Anti-seizure	0	1	1.00
Comorbidities	**Control**	**MHD**	**P-Value**
Hypothyroidism/abnormal thyroid stimulating hormone (TSH)	3	0	0.11
Polycystic ovarian syndrome (PCOS)	1	1	1.00
Type II diabetes	0	2	0.49
Triple X syndrome	0	1	1.00

Cardiovascular Health Comparisons

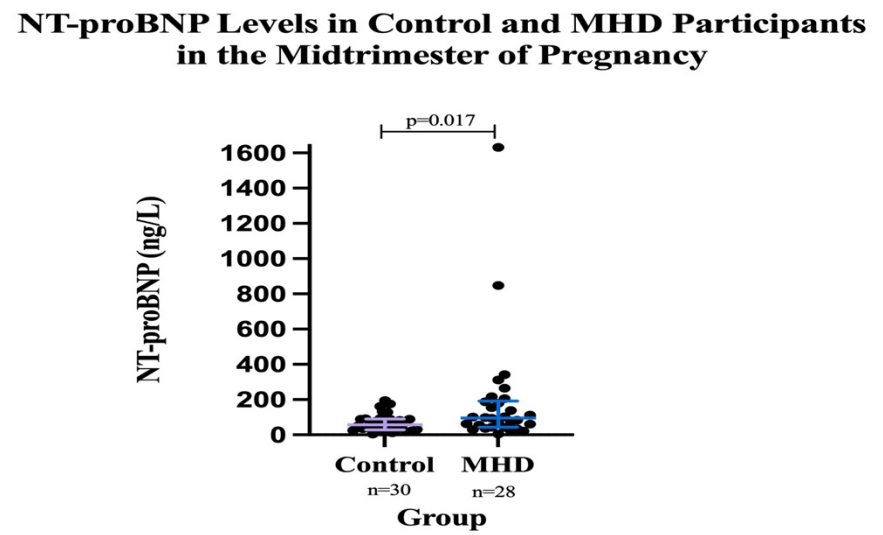
Baseline Cardiovascular Parameters

Baseline heart rate and systolic, diastolic, and mean arterial pressure were not different between groups (P>0.05) (Table 3-4).

Table 3-4: Baseline Cardiac Parameters in Control and MHD Participants			
Outcome	**Control (n)**	**MHD (n)**	**P-value**
Heart rate (bpm)	72±10 (32)	75±9 (33)	0.20
Systolic blood pressure (mmHg)	106±9 (32)	106±10 n=33	0.86
Diastolic blood pressure (mmHg)	68±6 (32)	66±6 (33)	0.91
Mean arterial pressure (mmHg)	81±7 (32)	79±7 (33)	0.34
NT-proBNP (ng/L)	58 [60] (30)	96 [139] (28)	**0.017**
All values are presented as mean ± standard deviation, except for NT-proBNP which is presented as median [IQR] since it did not present a normal distribution of data. NT-proBNP: N-terminal prohormone B type natriuretic peptide. Significance was defined as P<0.05.			

N-terminal prohormone B type natriuretic peptide (NT-proBNP) was significantly higher in MHD than control individuals (P=0.017), with 11 (33%) of those with MHD having levels above normal cut-offs (>125 ng/L) [251]. In the control group, five individuals (16%) had values slightly above normal cut-offs. In addition, 2 (6%) MHD participants had levels considered indicatory of heart failure or high myocardial stress (i.e. levels >450 ng/L) [207]. No control participants presented levels indicatory of heart failure. Even in the absence of the two participants with very high NT-proBNP levels in the MHD group, NT-proBNP was significantly higher compared to the control group (P<0.05). Although one of the participants with higher levels of NT-proBNP had a left ventricular ejection fraction (LVEF) close to 40%, none of the participants were considered to have clinical heart failure at the time of the visit. Blood work was not available for all participants. The distribution for NT-proBNP is demonstrated in Figure 3-1.

Figure 3-1: NT-proBNP Levels in Control and MHD Participants



NT-ProBNP: N-terminal prohormone B type natriuretic peptide. Individual values are shown with median and interquartile range.

Ventricular-Arterial Coupling and Primary Cardiac Outcomes

Ventricular-Arterial Coupling (VAC):

VAC calculations were performed for 64 participants and are presented as means and standard deviations (Table 3-5, Figure 3-2. A). VAC was significantly higher in MHD (0.78 ±0.15) than control (0.69 ±0.093) participants (P=0.0063). The different components of VAC (i.e. Ea and Ees) were compared between groups. Only the absolute Ees was different among groups (P=0.047) with a significantly lower value in MHD (1.7±0.42) in keeping with reduced left ventricular (LV) cardiac efficiency (Figure 3-2. B). Absolute Ea, Ea indexed and Ees indexed were not different between MHD and control participants.

In addition, the post-hoc power calculation analysis, as can be seen below yielded a power of 91% for the study of VAC, meaning that the sample size in the study was large enough to show significant differences among groups:

t tests - Means: Difference between two independent means (two groups)
Analysis: Post hoc: Compute achieved power

Input:
Tail(s) = Two
Effect size d = 0.846902
α err prob = 0.05
Sample size group 1 = 32
Sample size group 2 = 32

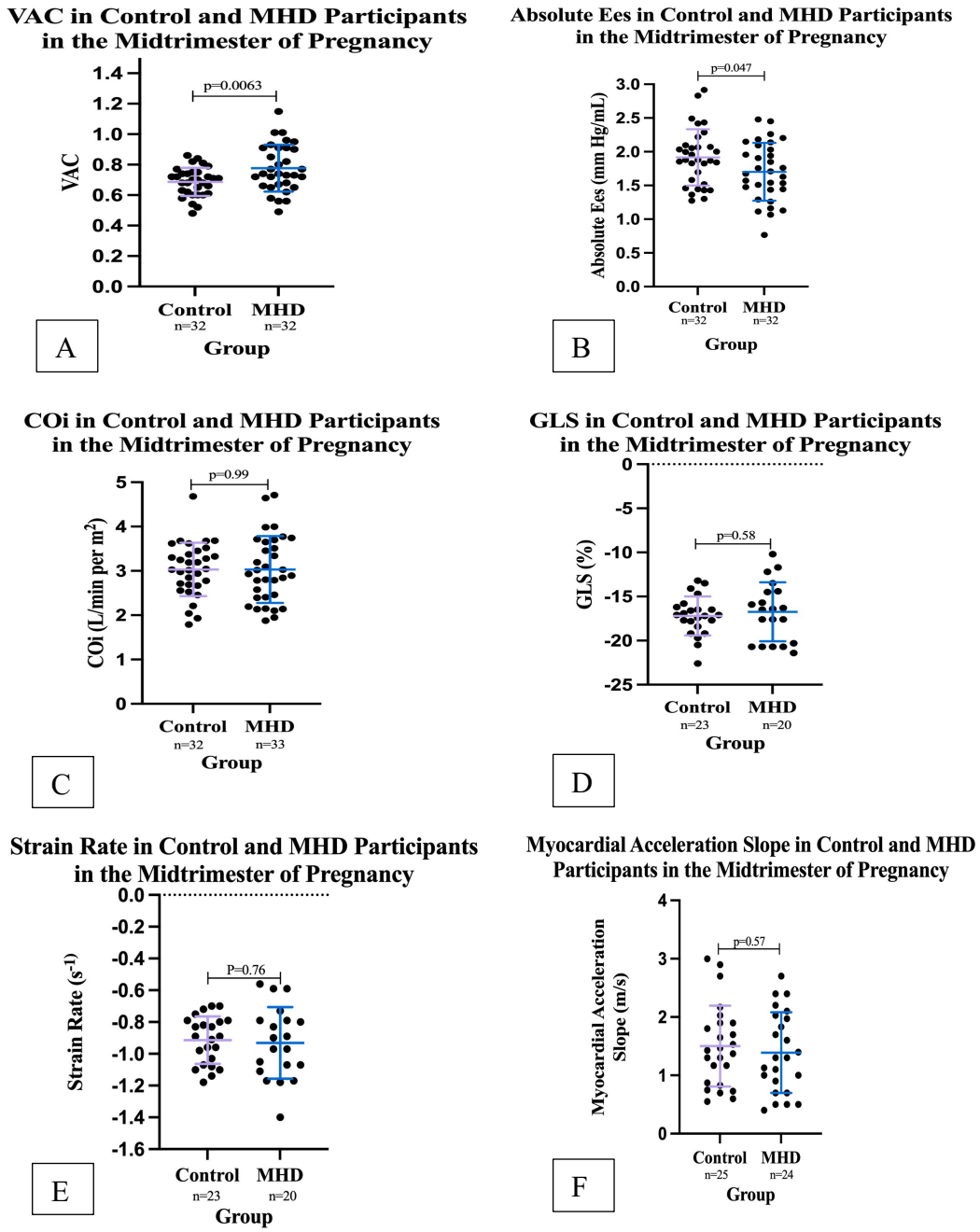
Output:
Noncentrality parameter δ = 3.3876080
Critical t = 1.9989715
Degrees of freedom = 62
Power (1-β err prob) = 0.9153908

Table 3-5: VAC and Primary LV Systolic Function Outcomes

Outcome	Control (n)	MHD (n)	P-value
VAC	0.69±0.093 (32)	0.78±0.15 (32)	**0.0063**
Absolute Ea (mm Hg/mL)	1.3±0.29 (32)	1.3±0.29 (33)	0.88
Eai (mm Hg/mL per m^2)	2.3 [0.60] (32)	2.3 [0.80] (33)	0.90
Absolute Ees (mm Hg/mL)	1.9±0.41 (32)	1.7±0.42 (32)	**0.047**
Eesi (mm Hg//mL per m^2)	3.4±0.82 (32)	3.2±0.90 (32)	0.27
Absolute CO (L/min)	5.57 [1.3] (32)	5.59 [1.4] (33)	0.85
COi (L/min per m^2)	3.03±0.60 (32)	3.03±0.75 (33)	0.99
GLS (%)	-17±2 (23)	-16±3 (20)	0.58
Strain rate (s^{-1})	-0.9±0.03 (23)	-0.9±0.2 (20)	0.76
Myocardial acceleration slope (m/s)	1.50±0.69 (25)	1.39±0.69 (24)	0.57

LV: left ventricle; VAC: ventricular-arterial coupling; Ea: arterial elastance; Eai: indexed arterial elastance; Ees: end-systolic elastance; Eesi: indexed end-systolic elastance; CO: cardiac output; COi: indexed cardiac output; GLS: global longitudinal strain. All values are expressed as mean ± standard deviation, except for Eai and absolute CO which are expressed as median [IQR] since they did not present a normal distribution of data. n= total participant numbers. Significance was defined as $P<0.05$.

Figure 3-2:VAC and Primary Cardiac Outcomes in Control and MHD Participants



A: Ventricular-arterial coupling. B: Absolute Ees (end-systolic elastance) C: Indexed CO (cardiac output) D: Global longitudinal strain. E: Strain rate. F: Myocardial acceleration slope. Individual values are shown with mean and standard deviation.

Cardiac Output and LV Systolic Function:

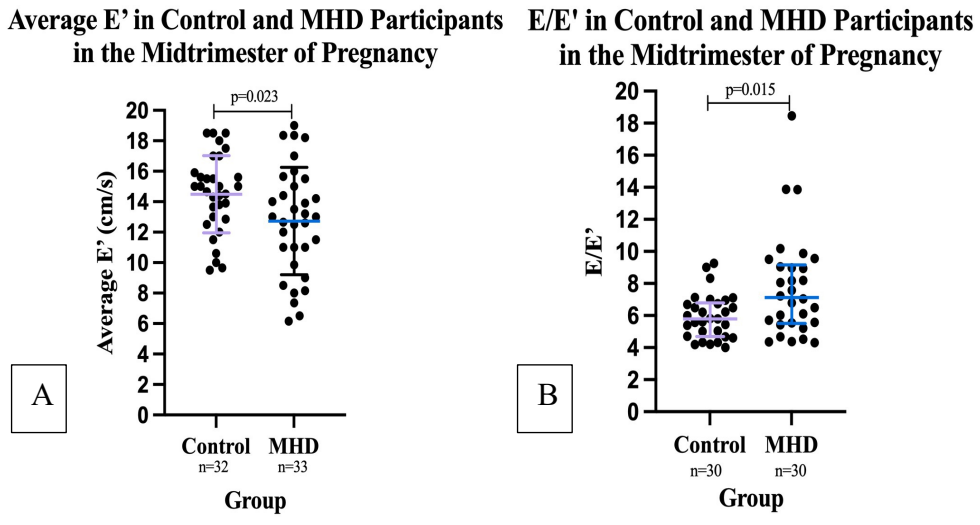
Both the absolute and indexed values for CO were not different between the MHD and control groups (P>0.05). Global longitudinal strain (GLS) (P=0.58), strain rate (P=0.76), and the myocardial acceleration slope (P=0.57) were also not significantly different between groups (Table 3-5, Figure 3-1). It was not possible to obtain some of these cardiac measures for all participants due to poor image quality, reducing the sample size for some of the outcomes.

LV Diastolic Function (Table 3-5):

End-diastolic volumes and mitral valve Doppler E wave peak velocities were not different between groups (Table 3-6). E/A wave peak velocity ratios were also not different (P=0.76) between MHD and controls. However, the average value for the annular myocardial velocities representing myocardial relaxation (average E') was significantly higher (P=0.023) in control (15±2.5) than MHD (13±3.5) participants. In addition, E/E' was significantly higher (P=0.015) in MHD (median [IQR]: 7.1 [3.7]) than control participants (median [IQR]: 5.8 [1.9]). As mentioned in the previous chapter, normal values for E/E' are <8 and E/E' >15 is indicative of increased LV filling pressures [234-236]. In the MHD group, 13 of 30 (43%) had E/E'> 8 and one presented with E/E'> 15. In the control group, only 2 of 30 (7%) had an E/E'> 8 and none presented with E/E'> 15. The distribution of these outcomes is presented in Figure 3-3.

Table 3-6: LV Diastolic Function Outcomes			
Outcome	**Control (n)**	**MHD (n)**	**P-value**
Absolute end-diastolic volume (mL)	83±15 (32)	89±17 (33)	0.11
Indexed end-diastolic volume (mL per m^2)	46±9.8 (32)	48±8.4 (33)	0.60
E (m/s)	0.84±0.16 (30)	0.91±0.21 (30)	0.18
Average E' (cm/s)	15±2.5 (32)	13±3.5 (33)	**0.023**
E/A	1.7 [0.8] (30)	1.6 [0.6] (30)	0.76
E/E'	5.8 [1.9] (30)	7.1 [3.7] (30)	**0.015**
LV: left ventricular. All values are expressed as mean ± standard deviation, except for E/A and E/E' which are presented as median [IQR] since they did not present a normal distribution of data. n= total participant numbers. Significance was defined as P<0.05.			

Figure 2-3- LV Diastolic Function Outcomes in Control and MHD Participants



A: Average E'. B:E/E'. LV: left ventricular. Individual values are shown with mean and standard deviation for E' and median and interquartile range for

Secondary Cardiac Systolic Outcomes

Stroke volume, ventricular volumes and left ventricular ejection fraction (Table 3-7)

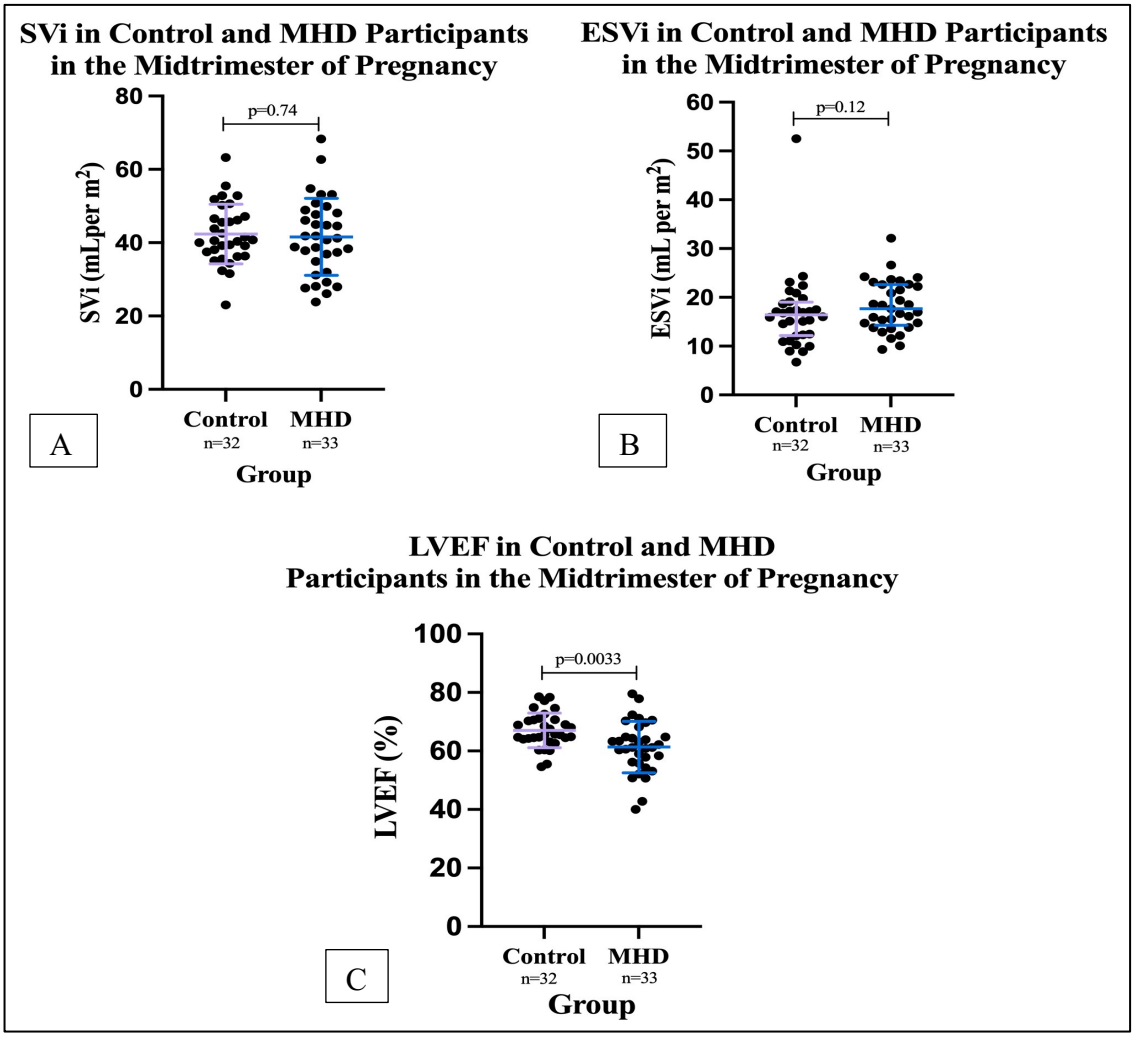
Stroke volume, both absolute (P=0.75) and indexed (P=0.74), were not different between groups. The absolute end-systolic volume was significantly higher (P=0.017) in MHD (median [IQR]: 34 [10]) than in the control group (median [IQR]: 28 [10]) but was comparable when indexed to BSA (P=0.12). However, the LVEF was lower in MHD (61±9%) than controls (67±6%) (P=0.0033). Those with cardiomyopathy appeared to have generally lower LVEF however, preliminary results showed that even after the exclusion of individuals with cardiomyopathy, LVEF was significantly lower in MHD compared to controls. The distribution of these outcomes can be observed in Figure 3-4.

Table 3-7: Secondary Systolic Cardiac Outcomes

Outcome	Control (n)	MHD (n)	P-value
Absolute stroke volume (mL)	76±15 (32)	77±19 (33)	0.75
Indexed stroke volume (mL per m^2)	42±8 (32)	42±11 (33)	0.74
Absolute end-systolic volume (mL)	28 [10] (32)	34 [10] (33)	**0.017**
Indexed end-systolic volume (mL per m^2)	16 [7] (32)	18 [8] (33)	0.12
LVEF (%)	67±6 (32)	61±9 (33)	**0.0033**

All values are expressed as mean ± standard deviation, except for absolute and indexed end-systolic volume which are presented as median [IQR] since they did not present a normal distribution of data. n= total participant numbers. Significance was defined as P<0.05.

Figure 3-4: Secondary Systolic Cardiac Outcomes in Control and MHD Participants



A: Stoke volume indexed (SVi). B: End-systolic volume indexed (ESVi). C: Left ventricular ejection fraction (LVEF). Individual values are shown with mean and standard deviation, except for graph B as it shows individual values with median and interquartile range given that it did not present a normal distribution of data.

Regression Analyses

A multilinear regression analysis was used to determine the influence of various outcomes of systolic cardiac function on VAC. Given that gravidity was significantly different between MHD and controls, it was also included in this regression analysis to determine its effect on VAC.

This is the only demographic variable included in the model given that it is usually the first variable considered during pregnancy and parity and losses are related to the latter, therefore, they could not be included in the model.

A model was created with select outcomes that showed no collinearity and that were believed to at least have a partial influence on VAC. The outcomes chosen included gravidity, GLS and E/E' as they were not already included in the equation used to calculate VAC (i.e. SV and LVEF). The model yielded an adjusted R^2=0.13, suggesting that the variables in the model did not have a high predictive ability on VAC (i.e. adjusted R^2 <7). This implied that other variables not included in this model would have influenced VAC.

Gravidity did not appear to have an effect on VAC as depicted by a P-value >0.05. GLS also did not show a significant effect on VAC. However, E/E' showed a significantly positive (P=0.039) influence on VAC (standardized B=0.015), suggesting that as E/E' increases, higher numbers potentially reflecting higher filling pressures, VAC increased (Table 3-8).

Table 3-8: Multilinear Regression Analysis for Gravidity and Selected Cardiac Outcomes and VAC

Outcome	Standardized B	Standard Error	P-value
Gravidity	0.008	0.017	0.65
GLS (%)	0.008	0.007	0.26
E/E'	0.015	0.007	**0.039**

Adjusted R^2: 0.13. GLS: global longitudinal strain. Significance was defined as P<0.05.

An individual regression analysis was also performed to evaluate the effect of VAC on NT-proBNP. VAC appeared to have a significant (P=0.008) positive effect on NT-proBNP (standardized B=0.343), suggesting that as VAC increases, perhaps reflecting increased cardiovascular mismatch, NT-proBNP will increase suggesting increased myocardial stress.

Table 3-9: Individual Linear Regression Analysis Evaluating the Effect of VAC on NT-proBNP			
Outcome	**Standardized B**	**Standard Error**	**P-value**
NT-proBNP	0.343	225.1	0.008
Adjusted R^2: 0.102. NT-proBNP: N-terminal prohormone B type natriuretic peptide. Significance was defined as P<0.05.			

Effect of MHD Severity on Cardiac Outcomes

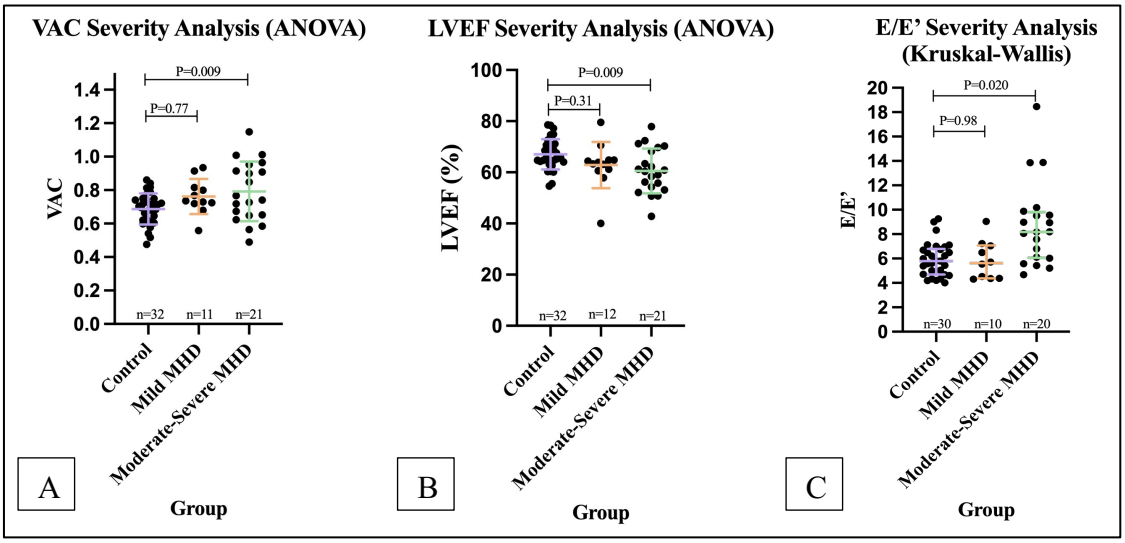
In total 12 and 21 MHD participants were considered to have mild and moderate-severe MHD respectively. Comparisons between MHD severity groups (control vs mild vs moderate-severe) showed that only VAC, LVEF, E' and E/E' were significantly different among groups when severity was considered (P<0.05) (Table 3-9, Figure 3-5). VAC was significantly lower (P=0.009) in controls (0.69±0.093) when compared to moderate-severe MHD (0.80±0.18), but not when compared to mild MHD (0.74±0.096), suggesting altered VAC is predominantly present in severe forms of MHD. LVEF was significantly higher (P=0.009) in controls (67 ± 6%) when compared to moderate- severe MHD (61 ± 9%), but not when compared to mild MHD (63 ± 9%). E' was significantly lower in those with moderate-severe MHD vs controls (12±3.3 vs 15±2.5, P=0.009). E/E' was significantly different between control (median [IQR]: 5.8 [1.9]) and moderate-severe MHD (median [IQR]: (8.2 [3.6]) participants (P=0.020). Findings were similar when only mWHO severity classification (I-II as mild and IIa-IV as moderate-severe) was used (data not shown) where significantly greater E/E' and VAC were found among those with more severe MHD. LVEF was similar among groups.

Table 3-10: MHD Severity Subgroup Analyses for VAC and Cardiac Outcomes						
Outcome	**Control (n)**	**Mild MHD (n)**	**Moderate-Severe MHD (n)**	**Test P-value**	**P-value control vs mild**	**P-value control vs moderate-severe**

VAC	0.69±0.093 (32)	0.74±0.096 (11)	0.80±0.18 (21)	**0.011**	0.77	**0.009**
Absolute Ea (mm Hg/mL)	1.3±0.29 (32)	1.3±0.33 (12)	1.3±0.31 (21)	0.99	1.0	1.0
Eai (mm Hg/mL per m^2)	2.4±0.65 (32)	2.3±1.9 (12)	2.4±0.65 (21)	0.80	1.0	1.0
Absolute Ees (mm Hg/mL)	1.9±0.41 (32)	1.8±0.40 (11)	1.7±0.45 (21)	0.13	1.0	0.15
Eesi (mm Hg//mL per m^2)	3.4±0.82 (32)	3.2±0.83 (11)	3.2±0.95 (21)	0.55	1.0	0.92
COi (L/min per m^2)	3.03±0.60 (32)	3.19±0.77 (12)	2.93±0.75 (21)	0.56	1.0	1.0
GLS (%)	-17±2 (23)	-17±4 (8)	-16±3 (12)	0.73	1.0	1.0
Strain Rate (s^{-1})	-0.9±0.03 (23)	-1.0±0.2 (8)	-0.9±0.2 (12)	0.38	0.78	1.0
Myocardial Acceleration Slope (m/s)	1.50±0.69 (25)	1.78±0.74 (10)	1.10±0.51 (14)	0.048	0.77	0.23
SVi (mL per m^2)	42±8 (32)	42±9 (12)	41±11 (20)	0.93	1.0	1.0
*ESVi (mL per m^2)	16 [7] (32)	16 [4] (12)	21[9] (21)	0.12	1.0	0.34
LVEF (%)	67±6 (32)	63±9 (12)	61±9 (21)	**0.01**	0.31	**0.009**
EDVi (mL per m^2)	46±10 (32)	45±4 (12)	49±10 (21)	0.28	1.0	0.73
Average E' (cm/s)	15±2.5 (32)	14±3.3 (12)	12±3.3 (21)	**0.009**	1.0	**0.009**
*E/E'	5.8 [1.9] (30)	5.6 [2.5] (10)	8.2 [3.6] (20)	**0.001**	0.98	**0.020**

VAC: ventricular-arterial coupling; Absolute Ea: arterial elastance; Eai: indexed arterial elastance; Absolute Ees: end-systolic elastance; Ees: indexed end-systolic elastance; GLS: global longitudinal strain.; SVi: indexed stroke volume; ESVi: indexed end-systolic volume; Coi: indexed cardiac output; LVEF: left ventricular ejection fraction; EDVi: indexed end-diastolic volume. All values are expressed as mean ± standard deviation given that an ANOVA was used for analysis, except for ESVi and E/E' which are presented as median [IQR] since they were analyzed with the Kruskal-Wallis test*. n= total participant numbers. Significance was defined as $P<0.05$.

Figure 3-5: MHD Severity Subgroup Analysis for VAC and Selected Cardiac Outcomes in Control, Mild MHD and Moderate-Severe MHD Participants



A: Ventricular-arterial coupling (VAC). B: Left ventricular ejection fraction (LVEF). C: E/E'. Individual values are shown with mean and standard deviation for A and B. Median and interquartile range is shown in C given that it did not present a normal data distribution.

Effect of Beta-Blockers on Cardiovascular Outcomes

Beta-blockers were used by some MHD participants (n=7). Therefore, the effect of beta-blockers, in addition to MHD, on various cardiac outcomes was evaluated with an analysis of covariance, that is a linear mixed model (Table 3-10). Some outcomes were shown to be influenced by this medication in addition to MHD. The results showed an effect on GLS (P=0.0067) and E/E' (P=0.006). LVEF was also shown to be influenced by beta-blockers (P=0.005) in addition to MHD. Although beta-blockers appeared to have an effect on VAC (P=0.048), They did not have an effect on either absolute and indexed values for Ea and Ees which determine the value of VAC. Given that beta-blockers are prescribed in more severe MHD lesions, it is hard to isolate the effect of this

medication on cardiovascular physiology from the pathophysiology associated with the specific cardiac lesion for which the medication was used.

Table 3-11: Analysis of Covariance for Beta-Blocker Use as Covariate for Various Outcomes of Interest

Outcome	P-value
VAC	**0.048**
Ea	0.70
Eai	0.33
Ees	0.29
Eesi	0.63
Coi (L/min)	0.31
GLS (%)	**0.0067**
ESVi (mL)	0.27
LVEF (%)	**0.005**
EDVi (mL)	1.0
E/E'	**0.006**

GLS: global longitudinal strain.; SVi: stroke volume indexed; ESVi: end-systolic volume indexed; Coi: cardiac output indexed; LVEF: left ventricular ejection fraction; EDVi: end-diastolic volume indexed. Significance was defined as $P<0.05$.

Uteroplacental and Fetal Outcomes

All values for uteroplacental and fetal outcomes were expressed as centiles, except for fetal heart rate.

Uteroplacental Outcomes

UtA pulsatility indices (PIs) were found to not be different between MHD and control groups in the midtrimester (Table 3-11). Examining the proportion of participants in each group with an abnormally high UtA suggesting increased downstream resistance, 3 (10%) of MHD versus 0% of controls had a UtA PI of >95th centile.

Although not reaching statistical significance (P=0.11) there was a tendency for higher UA PI values in MHD (median [IQR]: 83 [43]) compared to controls (median [QR]: 66 [31]). In addition, 7 (21%) MHD participants had measures >95th centile versus 5 (16%) of the controls for UA PI (Figure 3-6)**.**

Table 3-12: Uteroplacental Doppler Flow Patterns

Outcome	**Control (n)**	**MHD (n)**	**P-value**
Right UtA PI	18 [29] (27)	12 [66] (22)	0.98
Left UtA PI	23 [29] (31)	4 [74] (20)	0.94
Mean UtA PI	20 [28] (27)	8 [66] (20)	0.71
UA PI	66 [31] (32)	83 [43] (33)	0.11

UtA: uterine artery; PI: pulsatility index; UA: umbilical artery. Values are centiles expressed as median [IQR] given that they did not present a normal distribution of data. n= total participant numbers. Significance was defined as P<0.05.

Fetal Growth Outcomes, Heart Rate and MCA (Table 3-12)

Our results, expressed as median [IQR], showed centiles that were not different between groups for head circumference, femoral length and middle cerebral artery (MCA) PI (Table 13). Therefore, surrogates for fetal growth were not different between MHD and control participants at this point in pregnancy. Fetal heart rate did not differ as well.

Regression Analyses

Individual linear regression analyses were performed to assess the influence of VAC on the right, left and mean UtA Pis, as well as the UA PI.

Table 3-13: Fetal Growth Outcomes, Heart Rate and MCA

Outcome	Control	MHD	P-value
Head circumference	59 [58] (31)	57 [52] (32)	0.41
Femoral length	69 [34] (30)	69 [28] (32)	0.91
Fetal heart rate (bpm)	146 [10] (30)	145 [10] (32)	0.80
MCA PI	38 [53] (32)	49 [50] (33)	0.30

MCA PI: middle cerebral artery pulsatility index; bpm: beats per minute. Values are centiles (except for fetal heart rate) expressed as median [IQR] given that they did not present a normal distribution of data. Fetal heart rate is not expressed in centiles. n= total participant numbers. Significance was defined as $P<0.05$.

Our results showed that VAC as a model did not have a high predictive value, as depicted by an adjusted $R^2 <0.7$, for the right (adjusted $R^2 = 0.13$), left (adjusted $R^2 = 0.067$) and mean UtA (adjusted $R^2 = 0.14$), and UA PI (adjusted $R^2 = -0.009$). However, VAC did have a significant effect ($P<0.05$) on the right (standardized B=0.36), left (standardized B=0.29) and mean UtA PI (standardized B=0.40). The effect of VAC on the various measures of UtA PI appears to be positive, suggesting that as VAC increases so will the respective UtA PI (Table 3-13).

Table 3-14: Individual Linear Regression Analyses Evaluating the Effect of VAC on Various Uteroplacental Outcomes				
Outcome Influenced	**Standardized B**	**Standard Error**	**P-value**	**Adjusted R^2**
Right UtA PI	0.36	31.6	**0.01**	0.13
Left UtA PI	0.29	32.3	**0.04**	0.067
Mean UtA PI	0.40	31.2	**0.006**	0.14
UA PI	-0.085	25.8	0.50	-0.009
UtA: uterine artery; PI: pulsatility index; UA: umbilical artery. Significance was defined as $P<0.05$.				

MHD Severity and the Uteroplacental Circulation, Fetal Growth and Heart Rate

A Kruskal-Wallis test for non-parametric data was performed to conduct subgroup analyses to determine if MHD severity had an effect on the uteroplacental circulation and fetal outcomes. Uteroplacental and fetal outcomes were similar among groups when controls were compared to mild and moderate-severe MHD. This included the right, left and mean UtA PI, as well as the UA PI. As well, fetal growth parameters including head circumference, femoral length, MCA and fetal heart rate did not differ upon MHD severity analysis (Table 3-14).

Table 3-15: MHD Severity Subgroup Analyses for the Uteroplacental Circulation and Fetal Outcomes						
Outcome	**Control (n)**	**Mild MHD (n)**	**Moderate -Severe MHD (n)**	**Test P-value**	**P-value control vs mild**	**P-value control vs moderate -severe**
Right UtA PI	18 [29] (27)	12 [54] (8)	3 [56] (14)	0.99	1.0	1.0
Left UtA PI	23[29] (31)	48[79] (8)	3[50] (12)	0.52	0.71	0.83
Mean UtA PI	20[28] (27)	46[61] (8)	6[68] (12)	0.60	0.55	0.83
UA PI	66[31]	74[44]	83[87]	0.12	0.96	0.11

	(32)	(12)	(21)			
Head circumference	59[58] (31)	80[28] (11)	46[61] (21)	0.54	0.97	0.58
Femoral length	69[34] (30)	77[29] (11)	65[66] (21)	0.63	0.82	0.84
Fetal heart rate	146[10] (32)	141[10] (12)	146[10] (21)	0.26	0.70	0.63
MCA PI	38[53] (32)	39[44] (12)	49[48] (21)	0.48	0.52	0.77
UtA: uterine artery; PI: pulsatility index; UA: umbilical artery; MCA: middle cerebral artery. Bpm: beats per minute. Values are centiles expressed as median [IQR] given that they did not present a normal distribution of data. Fetal heart rate is not expressed in centiles. n= total participant numbers. Significance was defined as P<0.05.						

Effect of Beta-Blockers on Uteroplacental and Fetal Outcomes

The effect of beta-blockers on uteroplacental and fetal outcomes was evaluated (Table 3-15). The use of beta-blockers by certain MHD participants (n=7) showed no influence on any of the measures for the uteroplacental circulation or fetal growth in addition to MHD (P>0/05).

Table 3-16: Sensitivity Analysis for Beta-Blocker Use as Covariate for Various Outcomes of Interest

Outcome	**P-value**
Right UtA PI	0.45
Left UtA PI	0.82
Mean UtA PI	0.67
UA PI	0.72
Head circumference	0.95
Femoral length	0.61
Fetal heart rate	0.68
MCA PI	0.24
UtA: uterine artery; PI: pulsatility index; UA: umbilical artery; MCA: middle cerebral artery. Significance was defined as P<0.05.	

CHAPTER 4: DISCUSSION

As pregnancies complicated by maternal heart disease (MHD) are on the rise[1,2], an understanding of their cardiovascular adaptations in pregnancy and mechanisms responsible for increased maternal and fetal/neonatal complications [14, 20, 23,3,4] are critical for developing more effective management strategies and preventative interventions for this population. Our cross-sectional investigation provided insight, through the evaluation of maternal ventricular-arterial coupling (VAC) and cardiac function at 18-24 weeks of pregnancy, into how cardiovascular adaptations potentially differ between MHD and healthy pregnancies which could ultimately contribute to complications later in pregnancy. Further investigations of the uteroplacental circulation and fetal growth provided a deeper understanding about the relationship between cardiovascular function and the fetal-uteroplacental health in MHD at this time in pregnancy.

We found pregnancies complicated by MHD to demonstrate increased VAC in addition to decreased absolute left ventricular (LV) efficiency/function (Ees) compared to healthy pregnancies at 18-24 weeks. Indices of reduced cardiac function were concomitantly observed in MHD including decreased LV ejection fraction (LVEF) and increased E/E', the latter a noninvasive measure of LV end-diastolic pressure. Although most of these indices were within normal ranges, these subclinical changes could contribute to increased VAC. Despite these findings, less load-dependent measures of cardiac contractility (global longitudinal strain, strain rate, myocardial acceleration) and even cardiac output (CO) did not differ between MHD and controls in the midtrimester, findings which could explain the lack of clinical Doppler-based changes in the uteroplacental circulation and fetal growth at this point in pregnancy in the face of abnormal VAC.

VAC and Systolic Function

Our results supported our hypothesis that pregnancies complicated by MHD demonstrate increased VAC relative to controls in the midtrimester. To our knowledge, this is this first study to compare and observe a difference in VAC between MHD and healthy pregnancies. Although many were still within normal values for non-pregnant individuals (0.5-1.0<) [203], we found that pregnancies complicated by moderate-severe MHD [19-21], had the highest measures of VAC when compared to controls suggesting the mismatch between arterial load and LV efficiency is greater with increased severity of MHD. Previous work has demonstrated that VAC increases in the healthy pregnancy (without MHD) with increasing gestation [197], yet MHD participants had elevated VAC despite being evaluated on average at a slightly earlier gestational age than control participants, which further strengthens our findings of increased ventricular-arterial mismatch in MHD participants.

Although we also hypothesized that increased VAC in MHD would be associated with decreased cardiac output (CO), there were no differences in the absolute and indexed values for CO among groups at 18-24 weeks. Effective cardiovascular coupling allows for adequate CO, therefore, a mismatch of this coupling would have been expected to negatively impact CO and organ perfusion [252, 253]. It is possible the reduced cardiovascular coupling in MHD we observed was not sufficiently disruptive to affect CO at this point in pregnancy. It has been observed that in some severe types of MHD, such as in significant valvular disease or those with a Fontan circulation, the ability to increase CO in pregnancy might be limited with the most marked abnormalities found in the 3rd trimester [66, 74, 84]. Further work is required at this time to determine whether late gestational reduction in CO relates to greater cardiovascular mismatch particularly in more severe MHD, which would be suggested by the presence of a very high VAC. Those with

moderate-severe MHD in our study showed a lower CO than both controls and mild MHD, however, this did not reach statistical significance. Lack of significant differences in CO in our study could reflect generally a less severe MHD spectrum with a less severe cardiovascular mismatch that had not as yet affected CO, at least by 18-24 weeks of pregnancy. Although Wald et al [26] have previously observed a reduction in CO in MHD, this was isolated to MHD pregnancies with fetal and neonatal complications including prematurity, low birth weight and small for gestational age. In addition, the decline in CO in the latter study was observed only in the 3rd trimester in MHD pregnancies with those without neonatal complications. This could suggest that in MHD pregnancies with complications, there is a progressive lack of sufficient cardiovascular adaptation leading to reduced CO. Whether this fall in CO in the 3rd trimester of MHD pregnancies with maternal and fetal complications relates again to greater cardiovascular mismatch with consequent increasing VAC requires further investigation. Given the cross-sectional nature of our study with lack of correlation with eventual pregnancy and neonatal outcomes, we were not able to further examine the relevance of altered VAC despite normal CO in the adverse pregnancy outcomes. However, it is of note, when we examined MHD pregnancies based on residual disease and mWHO categories which relate to previously reported risks of maternal and fetal/neonatal complications, those historically of higher risk (categories II-III and higher) had the greatest cardiovascular mismatch in the midtrimester as depicted by increased VAC.

As VAC is the ratio between arterial load and left ventricular (LV) efficiency, an increased VAC can be due to decreased LV efficiency/function (Ees), increased arterial load (Ea), or a combination of the two [30]. We observed a significantly lower absolute Ees among MHD pregnancies suggesting decreased LV efficiency or function, perhaps as an important contributor to impaired cardiovascular coupling (i.e. increased VAC) in these complicated pregnancies.

However, we found absolute arterial load (Ea) to not differ between groups, suggesting once again, that the change in VAC at least at 18-24 weeks in MHD may be primarily due to decreased LV efficiency/function (Ees). However, given that Ea is calculated solely with the systolic blood pressure and stroke volume, a thorough assessment of parameters promoting increased arterial load such as increased pulse-wave velocity [172] and reduced vessel compliance [254] could provide greater insight into the role arterial load plays in MHD.

The reduction in LVEF observed among MHD pregnancies could further support some element of reduced systolic and overall cardiac function compared to control participants. Commonly, LVEF is an important clinically applied parameter of systolic function and has been used to assess the risk of heart failure and subsequent clinical outcomes including mortality [56, 213, 255]. The LVEF was 67 ± 6% in controls and 61 ± 9 % in all MHD which are both within the normal ranges for normal systolic function in non-pregnant females (54%-74%) [213], but could still indicate a reduction of systolic performance for the given loading conditions at that point in pregnancy. Further subgroup analyses showed that LVEF was significantly lower in those with moderate-severe MHD, but not with mild MHD, when compared to the controls. This suggests the presence of some element of decreased systolic performance, perhaps subclinical, with worse MHD possibly contributing to decreased LV efficiency (Ees), resulting in increased cardiovascular mismatch.

Given that LVEF is affected by preload, afterload and contractility, its reduction in MHD could have been impacted by increased arterial load, decreased LV contractility, or decreased end-diastolic volume [256]. In our study, arterial load (Ea), and end-diastolic volumes (surrogate of preload) were not different between MHD and control pregnancies. In addition, measures of contractility as depicted by global longitudinal strain (GLS), strain rate and myocardial

acceleration slope [49, 228, 256] were not different between groups. Given these findings, an isolated parameter may not be responsible for the decrease in LVEF in MHD. However, it is important to consider that the sample size was small for GLS measurements (n=20-23) and these measures were not available for all participants as image acquisition and quality was poor for some of the echocardiograms. We conducted a post-hoc power calculation with G power [250] with our current data which yielded a sample size of 100 per group to be able to detect differences in GLS. Therefore, it would be important to evaluate GLS with a larger cohort to determine whether it contributes to reduced LVEF in MHD. In addition, although LVEF is an important reflection of systolic function, given its load-dependency [213], the further study of GLS would perhaps provide more insightful information about contractility in MHD. It has previously been shown that GLS has a direct effect on VAC in settings of hypertension in non-pregnant individuals [257]. Hypertension is characterized by the presence of cardiovascular uncoupling resulting in a higher VAC [258]. In addition, reduced GLS (i.e. reduced contractility) has been previously associated with lower birth weight in late pregnancy in MHD suggesting that reduced contractility can affect fetal growth [25]. Thus, we could hypothesize that although reduced contractility was not observed in our study, it could be contributory to the increase in VAC present in MHD and could ultimately contribute to future poor neonatal outcomes in this population.

In our study, we also observed an increase in N-terminal prohormone B type natriuretic peptide (NT-proBNP) among MHD participants. NT-proBNP is released in response to myocardial wall stress and ischemia. It is a good predictor and more objective measure of heart failure [206]. It has been previously observed that NT-proBNP concentrations increase with decreasing LVEF in non-pregnant adult hospital inpatients [209], that is, NT-proBNP and LVEF are inversely related. Therefore, our findings of concomitant increase in NT-proBNP and reduced

LVEF in MHD could perhaps suggest the presence of increased wall stress. Wall stress is usually an indication of myocardial oxygen requirements and ventricular workload [259]. The reduction in LVEF in MHD could be due to persistent volume overload secondary to residual hemodynamic pathology such as valvular regurgitation [260] present in several of the MHD participants. This can increase ventricular workload or promote LV alterations occurring concomitantly with increased wall stress as depicted by increased NT-proBNP levels among MHD participants. A decrease in LV efficiency (Ees) as suggested by a decrease in LVEF which could then affect overall cardiovascular coupling (i.e. VAC) could be related to increased LV stress (i.e. increased NT-proBNP). This was supported by our linear regression analysis showing that VAC had a positive effect on NT-proBNP, perhaps suggesting that as there increased cardiovascular mismatch, LV wall stress will increase which can be indicative of increased ventricular workload and oxygen requirement [259]. If sustained, this increase in cardiovascular mismatch due to reduction in cardiac efficiency, perhaps related to a fall off the Frank-Starling curve [261], could translate into reduced CO which could result in fetal health deterioration [25, 262], previously observed in MHD pregnancies [20].

It Is important to note that previous literature indicating reduced cardiac function in MHD with neonatal complications [25, 26] and abnormal uteroplacental Doppler flow parameters [160] had cardiac parameters that showed cardiac function measures that were within normal ranges. Pieper et al [160] witnessed a decreased LVEF, despite largely normal values, and increased NT-proBNP among pregnancies with congenital heart disease (CHD), concomitant with impaired umbilical artery pulsatility and resistance indices (PI and RI, respectively) in CHD pregnancies compared to controls at 32 weeks of gestation. Therefore, the fact that our results thus far do not show clinically abnormal cardiac function, but rather lower cardiac function relative to normal pregnancies, cannot

be dismissed as perhaps even lower than normal cardiac function may be insufficient to maintain a healthy pregnancy and thus contribute to poor outcomes in this population later in pregnancy.

VAC and Diastolic Function

One of the main findings supporting our hypothesis of reduced cardiac function, especially at the level of the LV, in MHD was the presence of increased E/E', a surrogate for LV filling pressure [230, 232], [151]. Estensen et al [57] had previously observed preserved E/E' in all trimesters of healthy pregnancies, suggesting LV filling pressures remain relatively stable as pregnancy progresses, and despite greater CO demands. Although our study did not have longitudinal assessments of E/E', MHD had a higher E/E' than controls in the midtrimester. The values for E/E', as was true for LVEF, remained within normal values (E/E'<8) for 57% of the MHD participants, however an overall increased E/E' in MHD could still indicate more subtle differences in the LV myocardium contributing to impaired diastolic health in MHD [229]. This difference in E/E' was driven by participants with moderate-severe MHD when compared to controls. Melchiorre et al [263] previously assessed diastolic function in pregnancies without MHD, but that were complicated by fetal growth restriction. They used an algorithm to classify diastolic dysfunction where indications of lateral E'<14 (tissue Doppler velocity at the left side of the mitral valve) in addition to E/E' between 9-12 and other factors could indicate a "pseudonormalized" filling pattern. In our cohort, close to 25% of MHD participants had a lateral E'<14 and 28% exhibited E/E' ≥ 9. Importantly, 19% of controls had a lateral E'<14, but none had a calculated E/E' of ≥ 9. This could again suggest some degree of impaired diastolic function in MHD, although it might not yet be clinically significant. However, given that adequate LV filling is necessary for sufficient LV ejection, reduced diastolic function could contribute to decreased LV efficiency,

resulting in impaired or at least reduced cardiovascular coupling demonstrated by an increased VAC.

Several forms of adult heart disease, including repaired CHD, are known to be associated with LV diastolic dysfunction. Patients with functional single ventricle lesions who are status-post the Fontan procedure have been found to have occult diastolic dysfunction which can critically impact their unique circulation, one highly dependent on low-downstream filling pressures [264]. Although not always clinically evident, diastolic dysfunction has also been observed in other forms of heart disease including aortic [265] and mitral stenosis [266]. It appears that in settings of aortic stenosis, even in children and young adults, the LV can become stiffer and remodels resulting in increased hypertrophy and myocardial fibrosis [267] to compensate for an increased afterload [265]. In mitral stenosis, there can be reduced flow to the LV, resulting in decreased filling during diastole and increased left atrial filling pressures to accommodate for the resistance to flow [268]. Other conditions which are associated with increased preload and may also contribute to underlying myocardial diastolic dysfunction include aortic regurgitation [269] and mitral regurgitation [270], observed in several of the MHD participants in our study. Aortic regurgitation contributes to the LV end-diastolic volume [268]. During diastole, the regurgitant valve will allow retrograde flow from the aorta into the LV increasing volume load, resulting, most often, in LV dilation and eventual hypertrophy which can affect LV filling pressures [269, 271]. In settings of mitral regurgitation, blood from the LV will be directed to the left atrium which will eventually increase the amount of blood delivered to the LV during diastole [272]. The LV will dilate, becoming less compliant in response to increased volume being delivered from the left atrium [268, 270] which will negatively affect diastolic function. Furthermore, any underlying myocardial restriction, as may be seen in such conditions as left heart obstruction [74] and tetralogy of Fallot [273, 274], may be exacerbated with excess

preload, with higher filling pressures for a given preload. Therefore, a combination of intrinsic reduced diastolic function and increased loading due to residual disease could contribute to reduced LV efficiency and ejection, culminating in worsened cardiovascular mismatch and increased VAC. This speculation is supported by the findings of our multilinear regression analysis where E/E' had a positive influence on VAC, implying that as E/E' increases with greater diastolic function reduction, VAC also increased. This follows the principle that if the efficiency of LV filling is reduced, overall LV efficiency will be reduced, as depicted by lower Ees in MHD.

In addition, average E' was significantly lower in MHD than controls, especially in those with moderate-severe MHD. E' reflects mitral annular velocity during early ventricular filling, and a reduction in its value could indicate impaired LV dynamics that negatively impact early passive LV filling during diastole [229, 275]. This reduction in E' has been observed by Muthyala et al [276] in pregnancies complicated by preeclampsia, a complication observed more frequently in MHD pregnancies [20]. However, it is important to remember that preeclampsia is characterized by a higher afterload [277] and measures of E' are load-dependent [278]. Therefore, whether solely underlying myocardial dysfunction or increase in afterload, or both contribute to these abnormalities of LV function is unclear. It has been shown that myocardial relaxation which occurs following myocardial contraction and aortic valve closure [279] can be impaired by increased afterload in animal models [280]. That arterial stiffness is increased in various forms of CHD [27, 169], could subsequently contribute to these abnormalities. In animal models, it has been shown that increased afterload promotes myocardial remodeling, including fibrotic hypertrophy and apoptosis [281]. This could affect myocardial dynamics, including relaxation which could contribute to increased end-diastolic pressures and promote diastolic dysfunction [282-284]. Although Ea was similar between

MHD and controls in our study, further exploration of arterial load could provide clarity about its contribution to reduced diastolic function in MHD.

As mentioned previously, the end-diastolic volumes were not different between MHD and control pregnancies in our study. However, it has been shown that even in settings of diastolic failure, both end-diastolic and end-systolic volumes are normal at least in the non-pregnant individual [285]. In our study, reduced diastolic function, which can impact overall LV efficiency, was associated with increased VAC. The contribution of diastolic dysfunction to increased cardiovascular mismatch in MHD and its potential role in adverse pregnancy outcomes warrants further investigation.

Uteroplacental Circulation

Although increased VAC and reduced cardiac function were observed among MHD pregnancies, the uteroplacental circulation and fetal growth parameters were not different from control pregnancies. Our last hypothesis, as such, was not supported by our findings where we predicted indications of increased resistance to blood flow in the uteroplacental circulation (i.e. higher umbilical artery, UA, and uterine artery, UtA, pulsatility indices (PIs)) in MHD. Given that CO was not different among groups and perhaps gross measure of cardiac load (Ea), uterine perfusion was likely preserved in MHD pregnancies at this stage in gestation. It is possible that although there were other findings suggestive of reduced cardiac function in MHD compared to controls, the impact of reduced LV efficiency and its mismatch with the vascular system, as depicted by increased VAC, had not yet translated to reduced CO and therefore poor uteroplacental circulation and health in these participants. Following this principle, at least at 18-24 weeks of

gestation, blood flow was likely sufficiently delivered to the fetus, thus presenting similar growth parameters to control pregnancies.

Nevertheless, it is important to note that Doppler measures can have limitations. For the UA, Morris et al [286] performed a systematic review and meta-analysis and concluded that UA Doppler assessments are moderately accurate in predicting poor fetal and neonatal outcomes in high-risk pregnancies. However, some have argued that UtA Dopplers as a sole predictor have a poor accuracy at detecting risk for preeclampsia and intrauterine growth restriction [287]. For instance, Velauthar et al [288] found that in the first trimester of pregnancies without MHD, abnormal UtA velocity waveforms were only able to predict 47.8% of early-onset preeclampsia and 39.2% of fetal growth restriction. In addition, the placement of the pulse-wave measurement along the UtAs can either underestimate or overestimate PIs [289] which could provide an inaccurate reflection of flow and resistance dynamics. However, if pregnancies are low-risk and have less evident abnormal flow profiles, one could argue that these abnormalities might not yet be detected by Doppler assessments. Therefore, the lack of abnormal PIs in our study should be considered with caution as the Doppler assessments among those with MHD might not yet be able to detect subclinical uteroplacental abnormalities.

Beta-Blockers

It is important to note that a small number of MHD participants were treated with beta-blockers (i.e. Metoprolol and Labetalol) during their pregnancies. Beta-adrenergic receptors are used with the goal of decreasing blood pressure and heart rate [290, 291]. Beta-blockade therapy has previously been associated with intrauterine fetal growth restriction and small for gestational age

babies [291, 292]. However, in our study, heart rate, blood pressure and all outcomes of uteroplacental health and fetal growth were similar between MHD and control groups suggesting that the medication at that point in pregnancy had not affected fetal health. In addition, it has been shown that labetalol is safe to use during pregnancy and has not been associated with adverse neonatal outcomes [291, 293]. Metoprolol has also been shown to not impact fetal growth [294] and is one of the most frequently prescribed medications due to its lower risk of adverse outcomes [295]. We conducted a linear mixed model for covariance and used beta-blockers as a covariate with MHD in various outcomes of interest. Our results showed that beta-blocker use had an effect on VAC, GLS, LVEF and E/E'. However, the use of this medication did not have an effect on absolute or indexed Ea or Ees, therefore the mechanisms of its possible effect VAC are unclear. Given the small number of participants using this drug and the nature of the beta-blockers used by our cohort, we suspect these relationships do not necessarily relate to a causal impact of medication use but rather the cohort examined with those having more significant cardiac pathology receiving the therapy.

Implications of Findings

Our study has provided novel insights on the interaction between the cardiac and vascular systems in MHD through the assessment of VAC. As mentioned earlier, the number of pregnancies with MHD is on the rise [8] and will therefore become a more common challenge in the pregnant population. These pregnancies have a higher risk for preterm birth, preeclampsia, heart failure and maternal or fetal death in severe cases [14, 296]. Thus, it is important to understand contributing elements and further risk stratify. The only other study, to our knowledge, to evaluate VAC in MHD [33] did not have a comparator group and was therefore limited in its capacity to observe

differences in cardiovascular adaptations between MHD and healthy control pregnancies. In addition, no subgroup analyses were performed based on MHD severity which is relevant given more severe MHD is associated with worse maternal outcomes [14, 20]. Our study in the other hand, provided new information on differences in cardiovascular coupling between MHD and normal pregnancies. In addition, we carefully created categories for MHD severity based residual disease and on an important established risk stratification system (modified World Health Organization (mWHO)) [19-21] which allowed us to explore differences in VAC, in addition to cardiac function, between MHD and control pregnancies.

Given the observations in our study of reduced cardiovascular coupling in MHD (i.e. increased VAC) and indications of decreased cardiac function as depicted by reduced LVEF and E/E' suggesting decreased LV efficiency/function, we hypothesize these changes may set an affected individual up for complications later in pregnancy. That the changes observed were worse among pregnancies with more severe MHD recognized to have higher risks of maternal complications provides further support. In our study, we found higher VAC among those with more severe MHD, therefore, it could be predictive of future complications perhaps due to reduced cardiovascular coupling.

Additionally, reduced maternal systolic and diastolic function have previously been associated with obstetrical and fetal complications in pregnancies with and without MHD [25, 161, 276, 297, 298]. Reduced diastolic function, for instance, has been associated with fetal growth restriction [297], one of the more common complications observed in the MHD pregnancies. Although, we found decreased cardiovascular coupling in MHD, it might as yet not be severe enough to affect CO at this point in pregnancy, preserving fetal health. Whether this increase in VAC in these pregnancies is due solely to cardiac dysfunction and not arterial load remains

unclear. However, our results indicate an important cardiac contribution to this mismatch, at least in the midtrimester. Further studies are required to evaluate the role maternal vascular health plays in MHD as it has previously been seen to be affected in CHD [27].

VAC has previously been used to assess the severity of various conditions including heart failure, hypertension, and valvular disease among others, supporting its relevance in heart disease and providing a novel approach for risk stratification in these conditions [195, 200, 202, 299]. In addition, VAC has been shown to predict cardiovascular mortality in myocardial infarction in a manner comparable to BNP (B type natriuretic peptide) [203]. Therefore, our results suggest that altered VAC in MHD in conjunction with reduced cardiac efficiency (i.e. decreased Ees) in the midtrimester could herald future obstetrical and fetal complications in this population, and perhaps even cardiovascular risks. Some have also suggested using VAC to assess treatment response in various cardiovascular conditions given its ability to assess cardiovascular performance [195, 300, 301]. Since VAC can provide an indication of the severity of cardiovascular mismatch in pregnancies affected by MHD, as seen in our study, the targeting of individual elements of VAC, that is Ea, Ees or both, may ultimately be used to tailor therapy to prevent further cardiovascular mismatch and hopefully complications. In addition, the future implementation of VAC assessment in routine echocardiography-based exams for MHD pregnancies could provide rich insight into the state of cardiovascular coupling which could aid in risk stratification for this population.

Limitations

We acknowledge several limitations in our study. To begin, there were differences in the baseline pregnancy and pregnancy history characteristics of the groups. Despite attempts at

matching, gestational age at assessment, gravidity and parity were different between MHD and healthy control pregnancy groups. However, we did attempt to control gravidity through a multilinear regression model and saw that gravidity did not impact VAC in our study. Routine fetal echocardiography is usually offered for clinical indications to pregnancies at risk for fetal heart disease at 18-20 weeks, and, thus, this was when many of our MHD mothers were scheduled. Additionally, many were referred even in the first trimester and had exams at 10-14 weeks, ensuring scheduling early (18-20 weeks) for their follow-up scans. Scheduling for MHD pregnancies were always prioritized over control and lower risk pregnancies, with less aggressive earlier scheduling of the latter. It is of note, however, that while there were differences in the gestational ages at which the groups were seen (controls: 18.4-23.9 weeks and MHD: 17.9-23.4 weeks), the mean difference was 1.5-weeks which has less clinical relevance, and our findings of increased VAC in MHD participants was in contrast to normal trends in pregnancy, furthering supporting our findings [197]. There were differences with medication use among groups. For instance, beta-blockade therapy was used in the MHD group. However, this is a routine approach to the care of MHD pregnancies, making it difficult to study an affected cohort with MHD that does not include its use. The sample size was also a limitation in our study. A larger sample size would allow for the study of more MHD lesions, as well as more power for the analysis of various cardiac assessments that are sometimes difficult to acquire such as GLS and strain rate, and others with variability such as CO. A greater sample size would have permitted better patient matching between MHD and controls. In addition, this study was limited to the midtrimester and did not include neonatal and postpartum outcomes. Longitudinal changes of various outcomes of interest including VAC, CO, other measures of cardiac function, uteroplacental and fetal outcomes could not be studied which could provide insight on cardiac adaptations or maladaptations in MHD and

their consequences. Thus, the impact of altered VAC and cardiac function throughout pregnancy remains speculation.

Conclusion

MHD is associated with reduced cardiovascular coupling depicted by an increase in VAC at 18-24 weeks. It is also associated with decreased LVEF and increased E/E' suggesting decreased cardiac function among pregnancies affected by MHD particularly in those with moderate-severe MHD. Therefore, decreased cardiac function contributing to reduced LV efficiency is likely responsible for some of the cardiovascular mismatch observed in pregnancies complicated by MHD. That reduced VAC is found among those with worse MHD according to the mWHO risk stratification system, in addition to residual disease, could be predictive of future increased risk for maternal morbidity and mortality. Although uteroplacental and fetal health seem clinically preserved at 18-24 weeks among affected pregnancies, we speculate there may be subclinical changes at least in some or the evolution of changes that ultimately contribute to adverse pregnancy outcomes associated with MHD. The contribution of altered cardiac and vascular coupling to adverse pregnancy outcomes requires further exploration; however, that there are greater abnormalities witnessed in pregnancies with reported higher risks of complications, could intimate at a causal relationship.

Future Directions

This study was part of a larger longitudinal study which includes assessments in the third trimester and at 4-6 months postpartum. These longitudinal data should further elucidate relationships between maternal cardiac and vascular coupling and cardiac function and pregnancy

outcomes. There is still some debate as to whether VAC increases as normal pregnancy progresses given that some have suggested no change while others have demonstrated an increase in VAC [57, 198]. Therefore, a longitudinal analysis of VAC and how it differs between control and MHD pregnancies would provide further information on cardiovascular adaptations in healthy pregnancies and elucidate potential maladaptations in those complicated by structural and functional MHD. We suspect, if the CO demand is expected to remain high from the midtrimester to term with increasing mean arterial pressure and likely vascular resistance in the third trimester [6], there may be a greater divergence of VAC between MHD and health pregnancies, particularly for those with MHD who have poor pregnancy outcomes. This is also a time in which changes in uteroplacental health and fetal growth have been shown to become clinically manifested in MHD [26, 160]. An additional aspect of the prospective study includes pathological evaluations of the placenta from MHD studies that can be further correlated with third trimester findings and altered maternal cardiac and vascular coupling and cardiac function.

In this study, we evaluated various outcomes of cardiac function, gaining some understanding of the effect of MHD on Ees in the midtrimester. However, it would be important to also acquire various parameters assessing vascular health and arterial load (Ea). Arterial stiffness, for instance, has been shown to be reduced among non-pregnant individuals with HD who are physically active [302]. Although not included in the analysis, we have collected physical activity questionnaires to assess the level of activity among participants. Therefore, an evaluation of this information could provide insights on how exercise may impact VAC in MHD and healthy pregnancies in the midtrimester, as well as longitudinally. A proper assessment of arterial load or stiffness could be achieved by measuring pulse-wave velocities (PWV) which are an important indicator of arterial stiffness [172]. Flow-mediated dilation (FMD) is used to assess endothelial

response to ischemia, and could therefore be used to assess endothelial function in MHD [303]. The study of these parameters would allow for the compartmentalized analysis of the main factors affecting VAC, that is, arterial load and LV efficiency. In addition, Stoichescu-Hogea et al [257] recently showed that PWV/GLS is a good predictor for changes in VAC in hypertensive patients. They found an increase in ratio with increasing severity of hypertension and suggested its use in predicting VAC. It would also be important to increase the sample size of our cohort. This would allow for increased power for the analysis of various cardiac outcomes. However, most importantly, it would allow for the study of individual forms of MHD if sufficient participants are recruited. For instance, further subgroup analyses could be performed comparing relationships between cardiovascular coupling and cardiac function in right and left heart CHD and acquired heart disease. This would allow for an understanding of how the specific pathophysiology of a given form of cardiac disease can affect arterial load, LV efficiency and ultimately VAC. This is turn could potentially allow for risk stratification among participants and future treatment development to improve the cardiovascular health of affected individuals and their pregnancy outcomes.

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