Ventripoint Diagnostics Ltd.

Whitepaper

Prepared by

Ventripoint Diagnostics Ltd.

Introduction

The treatment of congenital heart disease requires regular check-ups and monitoring throughout a patient's life. Cardiovascular Imaging provides clinicians with vital information about functional and anatomical abnormalities that hold importance in clinical decisions. Regular imaging is needed to monitor the progression of possible worsening parameters, influencing the next decisions about the patient's treatment. The standard of care, in some cases, calls for a Cardiac MRI (cMRI). However, there are barriers that some patients, specifically children, have towards receiving a MRI scan. Some clinicians note a "practical cutoff" before a child will tolerate a cardiac MRI of around 10 years old without needing sedation of general anesthesia. This is because of the difficulty a young child has remaining still for an extended period of time, in an uncomfortable and noisy space. A key reason for CMR scans is the need for Right Ventricular assessment, part of what prompted the need for the VMS system and the Ventripoint solution. Subsequently, it was discovered that a quick, inexpensive alternative to cMRI has many benefits in other cardiac assessments.

This is even more true today with the age of COVID-19 and the lack of understanding of the effect of this disease on the Right Ventricle. The function of the VMS is to provide reliable data that would match a MRI scan, acting as a substitute or stand-in to a MRI. Cardiac MRI is considered the gold standard data for RV volumes and RV Ejection Fraction measurements, which are frequently required measurements in the management of adult and child patients with congenital heart disease. The VMS provides a clinician with a 3D model of the heart within the context of 2D image planes. By producing comparable metrics to a MRI, the VMS can be used to monitor RV volume and ejection fraction in these patients.

We sat down with one of our early adopters, Dr. Gregory Skinner, who runs the imaging clinic at the East Midlands Congenital Heart Centre in Leicester, UK. Dr. Skinner provided his insights and experience using VMS to scan patients with congenital heart disease.

Dr. Gregory Skinner MB BS MRCPCH

Dr. Skinner works as a Paediatric Cardiology Consultant, specializing in advanced echocardiography and cross-sectional imaging at Glenfield Hospital. Prior to this, he worked at EMCHC as a Specialist Registrar in Paediatric Cardiology. He is certified in Congenital Heart Disease Echocardiography by the European Society of Cardiovascular Imaging. Dr. Skinner runs the Imaging Clinic at the East Midlands Congenital Heart Centre (EMCHC) with his colleagues.

East Midlands Congenital Heart Centre

EMCHC is located close to the Leicester City Centre, in Leicester, UK. It is managed by the University Hospitals of Leicester NHS Trust. The hospital is nationally recognized for its medical care for heart disease, lung cancer, and breast care. EMCHC is closely associated with the heart centre at Glenfield Hospital which provides patients with advanced research and techniques including surgery with a Robotic Arm, TAVI (Trans-Catheter Aortic Valve Insertion) and the use of suture less valve in heart surgery.

Introducing VMS+

The VMS+ is point of care technology designed to create a 3D model of the heart from an echocardiogram and can obtain real time cardiac measurements in minutes.

The Ventripoint Medical System (VMS) is a medical imaging enhancement product that can be used to obtain volumes and ejection fractions of all four chambers of the the heart. A combination of both hardware and software, the VMS attaches to a conventional 2D cardiovascular ultrasound system and substantially enhances the ultrasound device's capabilities by creating an accurate model of the size and shape of all four chambers of the heart, which are utilized to produce MRI-equivalent analytical cardiac information on heart function. The system allows the clinician to view the 3D model of the heart in the context of the 2D image planes.

Cost-effective and Accurate Diagnostic Tool

The VMS+ is the first and only cost-effective and accurate diagnostic tool to measure the volume and function of the heart's right ventricle, which is particularly difficult to image with traditional ultrasound equipment due to its position just under the sternum and its complex shape. The advantage to the cardiologist is that this critical diagnostic function may now be performed in-house, utilizing standard ultrasound equipment, rather than referring the patient to an MRI facility. MRI is expensive and stressful to the patient, especially for children. Ultrasound is a relatively inexpensive modality but does exhibit issues with user variability, patient variability resulting in suboptimal images.

How it works

In practice, a position sensor system transmits the location of specific anatomical points within the heart to the VMS software. Utilizing a database of previously defined heart images, Ventripoint's proprietary artificial intelligent (AI) system uses a process called Knowledge-Based Reconstruction (KBR) to return a 3D model.

The Knowledge Based Reconstruction (KBR) algorithm leverages a MRI shape catalogue and anatomical landmarks from standard 2D echocardiogram images to construct a complete 3D model of the heart.

Accurate Cardiac Measurements

The measurements for volume and ejection fraction calculations for RV are obtained from sparse data. The mean percent difference between VMS and MRI results are within 10% for EDV, ESV, and EF with a 95% confidence.[Ref: clinical trial results]

Vendor neutral

The Ventripoint solution is vendor neutral and works with echo images generated from any ultrasound system, irrespective of the make or model. It is also less reliant on perfect image quality because the final measurements are derived from sparse data. Sparse data means that not every point in the image must be clear and resolved, the technology relies on fewer points in the image to resolve a measurement with accuracy. Unlike 4D ultrasound (for which RV assessment tools have been developed) VMS does not require all of the data to be acquired from one image. This means that optimal imaging can be achieved of all the necessary right heart structures. This is extremely challenging with 4D ultrasound, especially for patients with dilated right ventricles or poor acoustic windows.

VMS Experience

The Problem

In the case of cardiac imaging, ultrasound can provide limited and inconsistent data especially regarding the volumes of the four chambers of the heart and the amount of blood being pumped through those chambers. In most cases, cardiologists have traditionally referred their patients for a cardiac MRI (cMRI) which is the gold standard for the calculation of volumes and ejection fractions.

However, cMRI cannot be widely used given its limited accessibility in most communities, is significantly more costly than ultrasound, is time consuming (i.e. takes ca. 1 hour), may require the use of contrast media, and patients can find the scans distressing. This is particularly the case with younger children and adults with intellectual disability, who may require general anesthesia to be able to undergo a scan. However, with the Ventripoint system, most patients can be examined with inexpensive and readily available ultrasound equipment, producing MRI-quality data for volumes and shapes within the heart. The lower cost of the VMS+ means that a far greater number of patients, not only the difficult cases, can be evaluated at the level of the "MRI gold standard" for about the cost of an ultrasound exam.

The initial reason Glenfield Hospital had for purchasing the VMS+ back in 2015 was to be able to screen patients first, and then target patients who require an MRI scan. The VMS allowed Dr. Skinner and his team to see sudden changes in function or measurement, and be able to send that patient for an MRI Scan.

The Solution

The utilization of standard 2D echo equipment means that these advanced measurements can be determined in the echo department of a hospital and the patient does not have to be scheduled and moved to the MRI suite. This process is part of the standard echo exam with no extra cost to the institution.

VMS provides cardiologists and clinicians with the ability to monitor a patient over a period of time, providing a way to annually look at longitudinal changes. Often the change over time, as opposed to the absolute chamber size, is a more useful indicator of whether surgical or transcatheter intervention may be required. Doing this with MRI may be prohibitive, both from the availability and cost perspectives.

The system does not require the patient to lie completely still for an extended period of time, eliminating the need for sedation or general anesthesia. This saves time in the actual appointment, as well as makes necessary appointments easier for children and their parents.

VMS does not require perfect images. In cases where patients are difficult to image (i.e., due to patient size or poor acoustic windows), sufficient information can usually be gathered to determine the required volumetric measurement. The clinician has autonomy with images with multiple image views. Also, the learning curve for practitioners is not very steep and the solution fits into the existing echo exam workflow. Irrespective of the level of training and skill of the operator, image quality does not affect the accuracy of the results.

Congenital Heart Disease Discussed

Tetrology of Fallot

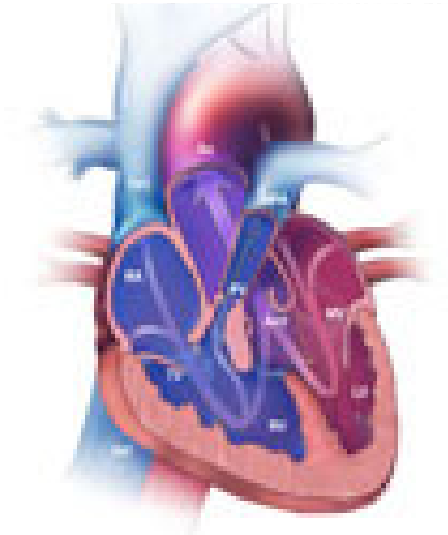
Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect that is diagnosed when the patient is an infant or young child. It is characterized by the combination of ventricular septal defect (VSD), right ventricular outflow tract obstruction (RVOTO), overriding aorta, and right ventricular hypertrophy. The combination of the VSD with the RVOTO leads to deoxygenated "blue" blood being shunted into the arterial circulation. This causes a characteristic bluish appearance of the skin, tongue and lips called "cyanosis".

For Dr. Skinner and his colleagues, TOF is one of the most common conditions that they see. The Centers for Disease Control and Prevention (CDC) reports that 1 in every 2518 babies born in the U.S. are born with TOF each year and accounts for 5 to 10% of all congenital heart disease [1]. Some babies may require a temporizing procedure when they are small to ensure that there is adequate blood flow to the lungs. The aim is to perform a full surgical repair between the ages of 4-6 months for most babies.

Due to the fact that the valve between the right ventricle and the pulmonary (lung) arteries is often small and malformed, frequently the surgical repair will involve an incision through the valve, with a patch being placed over this incision - a transannular patch (TAP). This means that the pulmonary valve is essentially absent in these patients, resulting in backwards flow when the heart is filling - pulmonary regurgitation (PR). It is not possible to implant an artificial valve at this age, as the baby would quickly outgrow it.

Following the operation, the patient's right ventricle needs to be closely monitored for the effects of the PR. Due to the need to be closely monitored, the need for accessible scanning is critical.

Despite improved outcomes due to early diagnosis and single stage repair in infancy, there are still severe complications that arise in adulthood. Many patients with TOF will have residual anatomic and hemodynamic abnormalities which lead to adult morbidity and fatalities. A common pathophysiological pattern is relieving obstructions in the right ventricle outflow tract and pulmonary valve causing pulmonary regurgitation2. Pulmonary regurgitation can lead to RV dilation and dysfunction, as well as the potential for LV dysfunction, aortic valve regurgitation, and other pathophysiologic issues.



How Do You Decide When to Do a Valve Replacement?

The right time to do a pulmonary valve replacement (PVR) comes with much debate, as described by Dr. Skinner. Replacing the valve at a younger age will likely mean that they will require an additional surgical procedure prior to adulthood as the valves have a limited lifespan (which seems to be shorted in younger patients). On the other hand, there seems to be a point past which the right ventricle does not recover or remodel after valve replacement.

If left for too long, the right ventricle becomes too enlarged and when the new pulmonary valve is put in, the patient's right ventricle will not be able to recover properly. For patients who have had the ToF repair as a child, 50% will require a reoperation, with pulmonary valve replacement being the most common operation [2].

Though a source of constant debate, the most common indications for pulmonary valve replacment are the presence of symptoms (e.g. breathlessness on exertion or dysrhythmias) and right ventricular volume parameters: indexed RV end diastolic volume >150 ml/m2 and indexed end systolic volume of over 80 ml/m2.

RV to LV end diastolic ratio of >2:1, or significant left or right ventricular dysfunction. The goal is for the RV to remodel post-operatively back to normal size and function. If you go far beyond these cut offs, you hit the point of no return and the right ventricle may not recover.

Volumetric data has traditionally only been available by performing cardiac MRI (cMRI) scans. The VMS+ enters this space because it can be used in the assessment of the timing for a valve replacement. Clinicians can scan and rescan at a later appointment to keep an eye on the patient's progression over time. In our discussion, Dr. Skinner says that Ventripoint provides comparable data, which is used to help monitor his patients over time. With the VMS+, Dr. Skinner can obtain the needed data more frequently than cMRI scans and can rely on the data both pre PVR (to help decide when PVR is indicated) and post PVR (to assess the RV remodeling process). This makes Ventripoint a very valuable tool in assessing these patients.

VMS Versus Simpsons and 3D for Volumetric Measurements

The Simpson's rule, or Biplane Simpson's Method, is a commonly used method of determining left ventricular volume and ejection fraction. The volumes are calculated from 2 orthogonal apical views of the left ventricle, using the summation of discs method. This makes significant assumptions about the 3D geometry of the left ventricle which often do not hold true in pathophysiological situations, such as when the right ventricle is dilated (as in patients following ToF repair with PR).

Accurate biplane Simpson's measurement requires alignment of the left ventricle centrally on echo views in 2 orthogonal planes. This is very challenging in many patients with poor echocardiographic windows (due to body habitus, lung hyper-expansion, etc.) or in patients with dilated right ventricles, in whom the cardiac apex is often displaced laterally to a point where is is not possible to achieve alignment. VMS allows the areas of interest to be interrogated from any achievable window and combining these to get accurate LV systolic and diastolic volumes and ejection fraction.

Many vendors have tools utilizing 4D acquisitions to measure ventricular size and function. These require the ability to scan the whole of the ventricle of interest from the same scan position. This is frequently impossible in patients with poor acoustic windows, and in some patients with severe right ventricular dilatation, it can be impossible to fit the whole of the heart into the scan cone. Again, by combining multiple images taken from different windows, VMS allows even the largest ventricles to be accurately measured.

Furthermore, the VMS system measures the volume of all the four chambers of the heart, a significant difference between VMS and Simpsons.

Usability

Due to Dr. Skinner and his team purchasing the first iteration of the VMS back in 2015, there were some limitations that came along with the system. One of the limitations was set up of the system, which required time to prepare the clinic room. Dr. Skinner and his clinic was able to work around this by scheduling time for set up between appointment times. The feedback Dr. Skinner and his team gave Ventripoint allowed us to create a more user-friendly version.

The VMS+ 3.0 version allows the system to be integrated into a clinic or hospital infrastructure, addressing the previous limitations. With this system, the VMS+ is simply wheeled into the appointment room and requires minimal setup. On his thoughts about the 3.0 version, Dr. Skinner expressed his excitement about using the system on inpatients, particularly those in the critical care unit. As well as the "very useful information on how to manage those patients".

Dr. Skinner and his clinic scan approximately 70-80 patients with the VMS each year

Reliability of VMS

Dr. Skinner typically sees referrals from paediatric congenital cardiologists for information on the size and function of the left and/or right ventricle. When asked about the receptiveness of the referred cardiologists on the VMS results, Dr. Skinner described a positive response. Dr. Skinner says, "I think we've spoilt them, I think they used to be surprised but now we are part of the furniture".

A single arm study was conducted where right ventricle measurements obtained using the VMS were compared to the gold standard cardiac Magnetic Resonance Imaging (cMRI) measurement in patients with Pulmonary Arterial Hypertension. The purpose of the study was to compare the VMS and MRI values for EDV, ESV, and EF and to determine VMS inter-observer and intra-observer variability (It is not within the scope of this paper to present and discuss the intra-observer and inter-observer variability data in detail.) The subjects underwent a 2D echocardiography according to standard of care. An additional 5 - 10 minutes of scanning using VMS transducer attached to the echocardiography system to acquire images for 3D reconstruction was required. Within one day of the VMS image acquisition the subjects also underwent cMRI according to hospital standards of care plus an additional 5 minutes to capture the PSSS required images. The primary endpoint of this study is the percent difference between the VMS and cMRI for estimating the end diastolic and end systolic right ventricular volumes (RVEDV and RVESV) in subjects with Pulmonary Arterial Hypertension (PAH).

The trial was defined as positive if the mean VMS-cMRI percent difference is <10% and >-10% at a 1-sided 0.025 statistical significance level for RVEDV and for RVESV, with no safety concerns for the VMS procedure. The study included 103 adult male (17) and female (84) patients aged 18-65 years and >= 65 years with Pulmonary Arterial Hypertension (PAH).

The interventional study was conducted in 7 centers in Canada and the United States. The study participants were assigned to a single group. 75 participants were analyzed and the following results were obtained:

- Percent Difference EDV: 4.80% (1.35)
- Percent Difference ESV: 1.76 (1.51)
- Percent Difference EF: 2.03 (0.66)

Being "part of the furniture" is how we want VMS to be integrated into clinical practice – with ease and with confidence. Dr. Skinner describes how when he had to do a MRI scan to monitor a patient, the metrics were comparable. A MRI has a 6% margin of error and the VMS results were within that range. In this example, the VMS system proves to be reliable in delivering metrics that match a MRI system. The commitment to effective and reliable data allows our users to scan patients with confidence.

Patient Experience

One of the difficulties of MRI scanning specific to children is the need for general anesthesia in order to complete the scan. A 15-90 minute period of not moving and laying completely still is unrealistic for a child and poses great difficulty. Due to this difficulty, anesthesia is required for a child to undergo a MRI scan. As well as being an unpleasant experience for both the child patient and parent, anesthesia is also an additional cost. The VMS+ does not require complete stillness for a period of time and only takes a few minutes to be scanned in the appointment room.

VMS+ system is a much more child-friendly experience than a cMRI.

The child's parents can also be present during the scan, which also makes the experience more comfortable for the child. Dr. Skinner noted that he was “pleasantly surprised” about being able to scan young children when first getting the system. The youngest patient Dr. Skinner has scanned to date is around two years old. Ventripoint improves the patient experience by creating a device that does not require complete stillness, long periods of time, and anesthesia.

Final Thoughts

When asked about his overall experiencing using VMS, Dr. Skinner described the system as “a very valuable tool”. He regularly gets referrals for it, which speaks to its usefulness and confidence in the data. Dr. Skinner also expressed the value of getting longitudinal information and how it is used in the decision making process about the patient.

Even though the VMS was initially used as a scanning process for getting patients in for MRI, Dr. Skinner's confidence in the VMS metrics speaks to the accuracy of the system. Looking ahead, optimizing the VMS+ system and the newest version for particular heart conditions will be what Ventripoint works towards.

"We have based decision making on doing surgery on the basis of the Ventripoint as well [as cMRI], so we’ve got a high degree of confidence." - Dr. Skinner

References

1. https://www.cdc.gov/ncbddd/heartdefects/tetralogyoffallot.html
2. https://academic.oup.com/ejcts/article/35/1/156/356489?login=true