Why do Doctors Need Knowledge Based Reconstruction?

Knowledge Based Reconstruction provides a method for rapid measurement of right ventricular volume and function in patients with congenital heart disease. Left ventricular volume can also be measured by the same technique. The measurements are made from either three-dimensional ultrasound or magnetic resonance images. The product will help physicians monitor their patients from clinic visit to clinic visit in order to detect when the heart is beginning to fail. Most importantly, Knowledge Based Reconstruction will help pediatricians choose the best timing for surgery. The product can also be used to evaluate how well a patient is responding to treatment.

To operate Knowledge Based Reconstruction, the user only needs to trace a few points on the images to mark the position of anatomic landmarks. This ease-of-use makes Knowledge Based Reconstruction faster and less expensive than currently available technology. This remarkable feat is possible because the software utilizes knowledge concerning the shape of the human heart and how it deforms in various disease states. The innovative concept here is that knowledge of three-dimensional heart size and shape is being harnessed to reduce the human workload required to accurately measure how well a patient's heart is functioning.

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1. Anatomy and Physiology of the Heart:

The heart is a mechanical organ. It pumps blood through the circulation. The heart has two main pumping chambers, the left ventricle and the right ventricle. The left ventricle generates a high pressure in order to pump blood through the systemic circulation (body). The right ventricle, which pumps blood through the lung, only has to generate a low pressure. The function of the heart is usually measured in terms of its “ejection fraction”, the proportion of the filled volume that is moved out in each heartbeat. Ejection fraction is calculated as (EDV-ESV)/EDV and expressed as a percent, where EDV=end diastolic volume (volume when heart is full) and ESV=end systolic volume (volume at end of contraction). Each ventricle has an inlet valve and an outlet valve. The valves ensure that blood flows only in the forward direction through the heart.

2. Importance of Ventricular Function for Patient Outcome:

Most of the research in cardiology has been focused on preserving left ventricular function because numerous studies have established its importance in determining prognosis for survival (1).

For many years the right ventricle was ignored because investigators thought it was simply a passive conduit directing blood from the body back to the lungs. Not until the 1970s did researchers realize that depressed right ventricular function influences survival in patients with congenital heart disease and in other conditions affecting the left or right ventricle or both. Recent studies have confirmed the importance of maintaining right ventricular function for all of the diagnoses scheduled for VentriPoint (2,3).

3. Measuring Ventricular Volume and Function from Cardiac Images:

Heart function is generally measured by analyzing cardiac images. There are several available imaging modalities. The physician chooses the modality based on both medical and practical considerations. Ultrasound (echo) is preferred for follow-up studies because it is inexpensive, does not expose the patient to ionizing radiation, is noninvasive and therefore safe, and is under the jurisdiction of cardiology (reimbursement goes to radiology for radionuclide ventriculography, magnetic resonance imaging (MRI), or computed tomography (CT)). These advantages must be weighed against echo's limitations: a) 15% of patients have image quality too poor for diagnosis due to chest anatomy characteristics; b) in the remaining patients image quality is influenced by the training and experience of the sonographer (technician acquiring the images). Cardiologists also perform angiography, but the cardiac catheterization procedure exposes the patient to the risks of radiation and having a catheter placed inside the heart as well as being expensive.

In addition to selecting the imaging modality, the physician must also select the method for analyzing the images. The left ventricle, with its regular shape, can be compared to an ellipsoid of revolution (4) in most patients except those with congenital heart disease (5,6). This approach is inaccurate when applied to the right ventricle due to its complex shape.

4. **What is Wrong with Current Methods for Measuring Right Ventricular Volume and Function:** In current clinical practice cardiologists evaluate the volume and function of the right ventricle by visual estimation from 2D echo images. Visual estimation is known to be inaccurate and poorly reproducible (7), but is nevertheless performed due to the unsuitability of all other methods:

   a. Angiocardiography was once the gold standard for measuring ventricular volume and function. This method is not practical for repeat follow-up evaluation because it is invasive, involves radiation, requires expensive equipment, and is extremely costly.

   b. Most echocardiologists estimate right ventricular size and function from 2D echo by visual inspection, i.e., “eyeballing” the images. They eschew quantitative methods since these all suffer from high error. The error comes from relating the right ventricle to geometric reference figures that poorly resemble the shape of this chamber. For example, the area-length and multiple-slice methods assume that the right ventricle has an ellipsoid shape or elliptical cross section, respectively. Neither method can accommodate the right ventricle’s irregular shape. A third method comparing the right ventricle to a pyramid was found more successful for pediatric patients, but the mean signed error in measuring volume was still high at 16% (8).

      Even in patients whose right ventricles fit a geometric shape, accuracy in measuring volume depends on the examiner’s ability to locate image planes that yield the maximal area and long axis length measurements. In addition there are no good landmarks in the right ventricle to help the sonographer find and image the same anatomy on follow-up studies. These problems are magnified when dealing with the variable right ventricular shapes seen in congenital heart disease.

   c. 3D echo is a relatively new invention. There are two modes. 1) In volumetric imaging, tightly spaced images are acquired to generate a solid volume of image data. To perform quantitative analysis from volumetric studies, the data set is cut into a series of parallel image planes. The user then traces the right ventricular contours in each plane and sums the volumes of the “slices”. This “Simpson’s rule” analysis is independent of geometrical assumptions so that even pathologically misshapen ventricles, as are commonly found in congenital heart defects, ought to be measurable with satisfactory accuracy. Volumetric 3D echo is available on commercial systems marketed by Tomtec, 3DechocTech (now GE), and Philips (Real-Time 3D™). However the right ventricle cannot be imaged in its entirety in most teen-age or adult patients because it doesn’t fit into the image sector (9). This problem persists in the latest model from Philips (ie33) even when the extended sector mode is used, which acquires the data set over 4 cardiac cycles, according to Drs. Sahn, Shirali, and Ge (with a lone dissent from Dr. Vannan).

      Furthermore the accuracy of volumetric techniques is inconsistent. One study reported accurate results when imaging cadaver hearts, but the authors traced right ventricular borders in as many as 49 parallel planes (10) (!) Another study

obtained good accuracy for measuring right ventricular volume at end diastole but not at end systole (both are required to measure function) even though they traced the right ventricular borders every 2 mm (20 borders for a normal-size adult heart) (11). Thus despite the time consuming image analysis, the accuracy for volume determination has not been consistent.

The second 3D echo approach is to acquire the images by routine freehand scanning while recording the spatial location and orientation of the image planes using a tracking system. The advantage of this approach is that the image data can be acquired from whatever combination of acoustic windows and views provides optimal image quality in any given patient. The borders of the heart structures are then traced in multiple views and used to reconstruct the surface of the right ventricle in 3D. The volume of the right ventricle is then computed from the 3D surface. Several techniques have been reported with good accuracy, but the right ventricular border has to be traced in 10-16 image planes (12,13). Munoz et al described a method that requires tracing the borders of only three images and extrapolating the right ventricular surface between them; however the required image planes are hard to find except in cadaver hearts (14). The piecewise smooth subdivision surface method developed by the University of Washington also requires that borders be traced in multiple views (15). Thus measuring right ventricular volume by 3D echo is accurate but not clinically feasible because of the difficulty of acquiring the images and/or the time required for analyzing multiple images to trace the borders.

c. Magnetic resonance imaging (MRI) is now considered the gold standard but MRI analysis is performed using the Simpson's method, as for volumetric 3D echo, and therefore requires time-consuming manual border tracing (16). MRI equipment is expensive and not generally available. According to the American Hospital Association, only 91 children's hospitals indicated that they had MRI services, although not all of the 175 members responded to the 2002 survey. The cost of each procedure makes it less suitable for serial studies.

   For these and other reasons, cardiologists do not refer patients for MRI. Of the 23 cardiologists whom we polled, only 5 expressed a preference for MRI for following their patients. Of these 5, 2 were actively involved in MRI research, and the other 3 pointed out the superior image quality that can be obtained from MRI while admitting the problems with scheduling and interactions with Radiology. Thus the overwhelming majority of cardiologists caring for CHD patients prefer echocardiography. MRI is the "gold standard" for research, but is not used in caring for patients with CHD.

d. Computed Tomography (CT) has recently been touted for providing excellent spatial resolution and visualization of coronary calcification and the coronary arteries themselves. However measurement of ventricular volume from CT images is a topic of research, requires manual border tracing, and is less available than MRI (17). Furthermore the heavy radiation dose required for CT imaging precludes its use for serial studies in children, especially because children are more susceptible to the tissue damaging effects of radiation than adults.

e. Radionuclide ventriculography: This modality has been touted for measuring both left and right ventricular function (ejection fraction) since the 1980s. Disadvantages are 1) it requires intravenous injection of a radioactive tracer, 2) absolute volume measurements are relatively inaccurate, and 3) it is difficult to distinguish the atrium from the ventricle. Indeed one researcher found no improvement in patients when measured by radionuclide ventriculography (18) but in later studies she and others found highly significant improvement when measured by echo or MRI (19,20).

f. Automated Border Detection (ABD): Research to develop ABD of MRI and echo images has been in progress for 1-2 decades. Some successes have been achieved for delineating the left ventricle. A major barrier to ABD of the right ventricle is the anatomy of this chamber. Its inner surface is covered by interlocking muscle bundles which produce an irregularly rough surface whose true base is difficult to delineate automatically. Also the complex shape of the right ventricle has prevented application of models commonly used to assist ABD of the left ventricle.

5. Clinical Need for Monitoring Right Ventricular Volume and Function in Congenital Heart Disease:

a. Their Hearts Fail Over Time, even after Surgery, Requiring Additional Operations: Approximately 32,000 babies (1%) are born each year with CHD. The majority of congenital anomalies affect the right ventricle. Modern surgical techniques have enabled most patients to survive childhood (21). Very few of the surgical procedures result in normal anatomy and physiology, however. In the patients with incomplete repair, the continuing hemodynamic abnormalities cause late complications. One survey of an adult congenital heart disease clinic found that from 1987 to 1997 "the incidence of reoperations has significantly increased, in keeping with progressive residual hemodynamic problems requiring reintervention" (22). The authors concluded that "these data clearly underscore the need for continuous follow up of adult patients with congenital heart disease… With the exemption of "benign lesions" … most patients with congenital heart disease would benefit from specialized follow up throughout their lives."

b. Monitoring the Right Ventricle Helps Detect Deterioration in Time for Surgery to Intervene – in Tetralogy of Fallot: For example, in tetralogy of Fallot, the most common congenital anomaly of the heart, the late complications of pulmonary regurgitation (leakage of the pulmonary valve) are heart failure, ventricular arrhythmias, and sudden death. These complications are related to enlargement of the right ventricle under the hemodynamic load (23,24). Such patients don't develop symptoms until very late in the course, after advanced and irreversible heart damage has occurred (25,26). For these reasons, "serial exercise studies and echocardiographic evaluation of right ventricular size are strongly advised to detect early right ventricular dysfunction" (27). These authors wrote "pulmonary valve insertion (surgery) should be performed as soon as evidence of progressive right ventricular dilatation and dysfunction is revealed, despite the absence of major symptoms." They further commented on the "difficult decision of balancing the risk of reoperation for repeated pulmonary valve insertion against the risk of allowing cardiomegaly (heart enlargement) to progress." Other investigators also found that "earlier pulmonary valve replacement prior to symptomatic manifestation showed beneficial effects" and recommended that timing of surgery be selected "according to objective evaluation of right ventricular function" (28). Other surgeons also voiced the dilemma in choosing the time of surgery: "Determining the appropriate time for pulmonary valve replacement (surgery) in patients … can be difficult. Ideally, all important anatomic lesions should be treated early to avoid deterioration of right ventricular function … However all bioprostheses (artificial heart valves) have a limited life expectancy,, and one would like to avoid surgery until it is clearly indicated" (29). They agreed that "prevention of progressive RV dilatation and dysfunction is a major reason for advising pulmonary valve replacement, even in the absence of symptoms." In other words, the key to optimizing patient management is measuring the right ventricle's size and function serially even though the patient is feeling well, because surgery should be performed as soon as this chamber begins to decline in order to avoid serious complications.

c. Monitoring the Right Ventricle Helps Detect Deterioration in Time for Surgery to

Intervene – Transposition of Great Vessels: In congenitally corrected transposition of the great vessels, which constitutes 14% of all anomalies, the right ventricle provides the body's circulation. This abnormally high load may eventually result in late heart failure, especially if there is concomitant valvular dysfunction. Van Son et al wrote, "we emphasize the importance of timely systemic atrioventricular valve replacement in corrected transposition to preserve ventricular function, and we suggest that operation be considered at the earliest signs of progression of symptoms or evidence of progressive systemic ventricular deterioration such as an enlarging ventricle and left atrium, development of pulmonary hypertension, and appearance of atrial arrhythmias. It is anticipated that improved monitoring of ventricular function with serial echocardiographic/Doppler hemodynamic assessment will result in further improvement of the long-term outcome of such patients (30)." A collaborative study of 19 institutions also recommended that "earlier surgical management of these patients before ventricular dysfunction becomes prominent should be incorporated into management in an attempt to improve long-term outcome. Patients with favorable anatomy, depressed RV function, and normal LV function should be considered for the double-switch operation" (31).

d. Monitoring the Right Ventricle Helps Detect Deterioration in Time for Surgery to Intervene – in Other Anomalies: Indeed all anomalies that call upon the right ventricle to support the systemic circulation have the same fate. Whether they have transposition of the great vessels (and Mustard operation) or congenitally corrected transposition of the great vessels or single ventricle (and Fontan surgery), these patients have "significant risk for heart failure accompanied by high mortality" and that mortality is predicted by depression of right ventricular ejection fraction (32). The authors further wrote, "This study suggests the importance of identifying this group of patients who are at risk for heart failure and considering strategies to preserve ventricular function". A review article also emphasized the importance of monitoring right ventricular volume and function quantitatively in order to optimize patient management, "The long-term prognosis of these patients … is mainly dependent on right ventricular function… New modalities of noninvasive follow-up are required which … allow for earlier detection of pressure or volume overload of the right ventricle, prior to the occurrence of failure or irreversible myocardial damage. Early detection of right ventricular failure may permit better medical management and a better insight as to the optimal timing for preventive surgery" (33).

The bottom line**: Accurate serial volumetric assessment of the right ventricle is important because it will enable earlier recognition of impending right heart failure. By providing these measurements, the VentriPoint product helps physicians intervene in time to improve these patients' long-term prognosis and quality of life.**

Knowledge Based Reconstruction Solves this Clinical Need:

a. KBR is based on the piecewise smooth subdivision surface reconstruction method, the most anatomically accurate 3D surface reconstruction method reported to date and the only reconstruction method proven to provide faithful representation of 3D shape as well as accurate volume (15,34).

b. KBR is fast (takes 2-3 minutes per volume measurement). The user provides only a very sparse input of points (not whole borders). The user can choose the highest quality images to trace those points. In other words, the user is free to work just on the images where each part of the ventricle is best seen.

c. KBR does not require tedious tracing of whole borders. Border tracing is hard because the images rarely show the entire border clearly; there is always some part that is fuzzy and hard to identify. Border tracing takes so much time and effort that cardiologists hesitate to trace even one or two borders for a left ventricular volume. They never trace the 8 or more borders required for a right ventricular volume.

d. KBR leverages the accuracy achieved from the sparse input by utilizing a knowledge database. The database embodies knowledge of the shape of the right ventricle and how much that shape varies in human disease. The knowledge database constrains the software to produce heart-like reconstructions and prevents the generation of strangely shaped surfaces.

e. KBR was cited by a recent review article as a solution to the need for better monitoring of the right ventricle (3).

f. KBR works! Dr. Sheehan's pilot study of 9 patients with tetralogy of Fallot, a common congenital anomaly, will be presented at the annual scientific meeting of the American Society of Echocardiography in June, 2005. The results of this analysis showed excellent accuracy of KBR for measuring right ventricular volume at both end diastole (EDV) and end systole (ESV):

	True	KBR	Error	% Error	p*
EDV	331 ± 156	327 ± 147	5.1 ± 29.5	-0.4 ± 29.4	NS
ESV	247 ± 140	239 ± 134	-8 ± 11	-2.9 ± 4.3	NS
EDV + ESV combined		r=0.99 SEE=22 ml (6.9% of mean) true volume = 0.94*KBR volume+9.8			

g. KBR has also been validated and published for measurement of left and right ventricular volume in adult acquired heart disease (35,36). This is important for VentriPoint's pipeline of products (see below).

7. Importance of Measuring Left Ventricular Volume and Function in Congenital Heart Disease

It is also important in most patients to measure the volume and function of the left ventricle. One cardiologist said, “I want to know the left ventricular function of all of my patients who get right ventricular studies.” After all, the left ventricle is the heart’s main pumping chamber in all but a few rare congenital anomalies, so physicians need to know whether it is diseased or failing.

Alternative methods are available for this. However VentriPoint’s product for the right ventricle will also provide fast and accurate measurement of left ventricular volume and function from the same image data. This means that the user does not have to repeat either the imaging or the image selection steps if the physician orders both ventricles analyzed. VentriPoint thus provides a one-stop shop.

8. Need for Monitoring Left Heart Status in Leukemia

Acute lymphoblastic leukemia is usually treated by a cocktail of four chemotherapeutic drugs. Unfortunately one of these drugs is toxic to heart muscle. Left ventricular function must be measured before treatment is begun and monitored at regular intervals throughout treatment. Even after successful remission is achieved follow-up studies need to be performed regularly for years. This is because these patients may develop heart failure as late as two decades after surviving the leukemia.

The number of new patients with acute lymphoblastic leukemia each year is small, and KBR will be competing against the existing methods for evaluating the left ventricle. However VentriPoint has chosen acute lymphoblastic leukemia as the next diagnostic product after congenital heart disease because the pediatric echocardiologists who evaluate acute lymphoblastic leukemia patients are the same as those who care for congenital heart disease patients. The familiarity of KBR to these physicians will make the leukemia product easier to introduce.

9. The Case for Pulmonary Hypertension

Pulmonary hypertension (PH) means elevated pressure in the lung circulation. According to CDC statistics, there were 174,854 hospitalizations among persons with pulmonary hypertension in 1998. PH is most commonly caused by disease of the left side of the heart or of the blood vessels to the lung (such as thromboembolism ie blood clot to lung). Pulmonologists refer their patients to adult echocardiologists for echo evaluation both to establish the diagnosis and to determine how severely the heart is affected. PH patients require treatment if they develop right ventricular enlargement and failure. Most are quite sick and require very close follow-up, as often as every 3 months. The "median survival after diagnosis of primary PH is 2.8 years, but patients who do not develop right heart failure may survive for more than 10 years. For patients with secondary PH the prognosis depends on the underlying disease as well as on right ventricular function. For instance, patients with chronic obstructive pulmonary disease (smoker's lung) and moderate airflow obstruction have only a 50:50 chance of living three years once they develop right ventricular failure." As one surgeon wrote, “Diagnosis of right ventricular dysfunction is difficult, but of great clinical importance in patients with chronic right ventricular pressure overload due to pulmonary embolism. A more accurate estimation of right ventricular function in these patients might be useful in the determination of the optimal moment for medical or surgical intervention in order to prevent or delay irreversible right ventricular failure” (37).

As VentriPoint’s third diagnostic product, measurement of right ventricular volume and function for PH introduces KBR to mainstream adult cardiologists.

10. Heart Failure: the Focus is Shifting to the Right

There are 2,400,000 admissions to the hospital in the United States annually for patients with heart failure. As for pulmonary hypertension, heart failure can have different causes. However the bottom line is the same – the heart muscle is unable to perform its duty of propelling enough blood forward through the circulation. Traditionally cardiologists focused their attention solely on the left ventricle when evaluating their heart failure patients. However a number of recent studies have shown the importance of the right ventricle as well. Therefore VentriPoint will provide both left and right ventricular analysis for this diagnosis. Measurement of right ventricular function not only defines the patient's chances of surviving, but also provides physicians with a test that they can use to guide treatment. Access to the right ventricle, and prior experience with the pulmonary hypertension product are both anticipated to enhance physician acceptance of KBR for the left ventricle in this patient population.

- Right ventricular ejection fraction impacts survival in heart failure of unknown etiology (38).
- In heart failure due to coronary artery disease, "Mortality was significantly greater among patients with a depressed right ventricular ejection fraction" (39).
- Regardless of the cause of heart failure, "right ventricular function is a crucial determinant, indeed the single most important predictor, of short-term prognosis…This variable allows a useful risk stratification … and provides guidance in the assessment of indications and timing for transplantation" (40).
- The leading cause of death is development of right ventricular failure in patients in whom a left ventricular assist device (artificial heart pump) is implanted (41).

11. The U.S.'s #1 Killer: Coronary Heart Disease

Heart attacks strike more than 1 million Americans each year. A heart attack occurs when one of the blood vessels supplying a person's heart muscle is closed off by atherosclerotic plaque. The starved muscle dies within minutes, leaving a scar that cannot contribute its share to the function of the heart. Heart attacks involving the front of the heart tend to be larger, cause more muscle damage, and often lead to chronic heart failure if the patient survives. In contrast, heart attacks involving the inferior wall of the heart are smaller and less risky.

Recent studies have shown that when the right ventricle is involved, even heart attacks involving the inferior wall can be dangerous. "Right ventricular infarction (heart attack involving the RV) defines a high-risk subgroup of patients with inferior left ventricular infarction (who normally have relatively low risk)" (42). This problem is more common than previously thought: "Right ventricular ischemia (temporary lack of blood supply) occurs in 50% of patients with acute myocardial infarction (heart attack) and may result in heart failure associated with poor outcome (43).

As for heart failure, the VentriPoint product for coronary artery disease will provide for both left and right ventricular analysis, with the anticipation that physicians' prior experience with KBR for the preceding products will lead them to perform KBR on coronary patients as well.

12. Additional Diagnoses to Target in the Future

The products discussed above were chosen after consideration of the physician's need to have the measurement as well as the market size. New applications for KBR are still being identified as we continue to canvas physicians and search the medical literature. These will be considered in time as the market for KBR develops and matures.

- In acute respiratory distress syndrome, which is the most severe form of acute lung injury, the average mortality is 50%. Right ventricular dysfunction is one of four variables found to be independently associated with an elevated risk of death (44).
- In valvular heart disease "the importance of the right ventricle as a determinant of clinical symptoms, exercise capacity, peri-operative survival, and postoperative outcome has been underestimated for a long time" (45).
- Myocarditis is a disease of heart muscle that can mimic coronary artery disease. The likelihood of an adverse outcome, defined as death or need for heart transplantation, was greater in patients with abnormal right ventricle function" (46).

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