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DEPARTMENTS




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## NESIRITIDE, A NEW DRUG FOR CHILDREN WITH HEART FAILURE

*By Jennifer Carbone Zuccaro, MD*

Pediatric therapies are often "borrowed" from adult medical regimes. Nesiritide has recently been added to mainstream medical treatment of adult heart failure patients. Pediatric experience with this drug to date is extremely limited, and nesiritide is unknown to many pediatric cardiology practitioners. This article is designed to familiarize pediatric cardiologists with this new and promising drug, now entering the pediatric therapeutic arena.

***"Thus far, there is minimal experience in pediatrics and no published data in the pediatric literature that describes the safety or efficacy of nesiritide."***

### Background

With the discovery of secretory granules in guinea pig atria in 1956, the heart was determined to be an endocrine organ. Subsequent experiments led to the identification of atrial natriuretic peptide (ANP) in 1984. Since then, there has been the discovery of at least two other natriuretic peptides: Brain (B-type) natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). While ANP and BNP are more similar in structure and are produced predominantly in the myocardium, CNP is produced mostly in the central nervous system and is found in low concentration in the plasma. In a normal hemodynamic state, ANP and BNP are produced in the atria. However, in response to ventricular stretch (left more so than right), the ventricular myocardium will synthesize BNP in greater quantity. (1)(2)

### Mechanism of Action

ANP and BNP have similar actions on multiple target organs. There are three receptors for the natriuretic peptides (A, B, and C) located on the membrane surface of their target cells. ANP and BNP bind preferentially to receptor A, which is linked to the cyclic-GMP dependent cascade. Receptor B is also linked to the c-GMP pathway, but has a higher affinity for CNP. Receptor C is a clearance receptor. Their cardiovascular effects lead to a decrease in vascular tone and subsequent reduction in preload. This is accomplished via receptor mediated dilatation of both the arterial and venous vasculature as well as suppression of the sympathetic nervous system. At the renal level, the natriuretic peptides cause an afferent dilatation and efferent constriction of the renal arterioles leading to an increase in glomerular filtration. They also inhibit sodium reabsorption at the tubular level for a net effect of increasing diuresis as well as natriuresis. Another mechanism for accentuating diuresis is through their inhibition of the renin-angiotensin-aldosterone axis and antagonism of vasopressin.1, 2 BNP has been shown to decrease the production of endothelin-1, a peptide secreted from endothelial cells which causes vasoconstriction and sodium retention.3 Lastly, the natriuretic peptides act at the level of the central nervous system to decrease sympathetic tone and inhibit salt appetite and water drinking.(1)

### Nesiritide

Nesiritide is a recombinant human BNP manufactured from E. Coli with the same amino acid sequence as endogenous BNP. This is the first new drug in more than a decade to be approved by the Food and Drug

Administration (FDA) for use in decompensated congestive heart failure (CHF).1 The dosing is currently recommended as a 2mcg/kg bolus followed by a continuous infusion of 0.01mcg/kg/min. The dose may be adjusted by giving a 1mcg/kg bolus and increasing the infusion by 0.005 - 0.01mcg/kg/min to a maximum of 0.03mcg/kg/min. A three hour time period is recommended between increasing the dose as 95% of the systemic blood pressure effects will be notable by then. The half-life in patients with CHF is approximately 18 to 20 minutes with the effect dissipating within 2 to 4 hours. The main form of clearance is via the C receptor that internalizes the peptide, which is then degraded. Secondly, circulating BNP is inactivated by a neutral endopeptidase. Lastly there is minimal renal clearance.(4)

*"We have seen no major complications and are currently compiling the data for a retrospective safety review."*

**Clinical Trials**

Nesiritide has been studied in over 1500 adult patients with decompensated CHF. The Vasodilatation in the Management of Acute CHF (VMAC) trial is a multicenter, randomized, double-blind trial of 489 patients comparing treatment with nesiritide vs. nitroglycerin in patients with decompensated CHF. Their results showed a decrease in pulmonary capillary wedge pressure (PCWP) which was significantly greater in the nesiritide group vs. placebo and vs. nitroglycerin.(5) Another study by Colucci et al found a decrease in PCWP, right atrial pressure (RAP), and systemic vascular resistance (SVR) that was dose dependent. Unlike the VMAC trial, this study noted an improvement in global clinical status and reduced dyspnea and fatigue in comparison to placebo.(6) While nesiritide has been shown to decrease SVR and preload, it does not cause a reflex tachycardia and is not arrhythmogenic. In the Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy (PRECEDENT) trial, it was shown that nesiritide did not increase the heart rate and either reduced or had a neutral effect on ventricular ectopy when compared to dobutamine.(7)

**Adverse Effects**

In the studies thus far, nesiritide has been shown to have very few side effects. The most common is a dose-dependent hypotension, which is usually mild or asymptomatic. In the VMAC trial, there were fewer total adverse events in the nesiritide group than the nitroglycerin group.5 In the Colucci study, after 6 hours 2% of patients receiving 0.015mcg/kg/min and 5% of patients receiving 0.03mcg/kg/min experienced symptomatic hypotension. In longer-term therapy (up to 7 days) these numbers increased to 11% in the low dose nesiritide group and 17% in the high dose group. However, in this study, the dose was started at 0.015 or 0.03mcg/kg/min and not increased incrementally as suggested.(6)

**Pediatric Experience**

Thus far, there is minimal experience in pediatrics and little published data in the pediatric literature that describes the safety or efficacy of nesiritide. One study by Sehra and Underwood from Loma Linda reviews 10 uses of nesiritide in 7 patients awaiting heart transplantation. They found that there were no changes in systolic blood pressure related to nesiritide use, and that urine output improved by 24%. We have used nesiritide in approximately 40 pediatric patients for a variety of reasons ranging from dilated cardiomyopathy, to congenital heart disease for afterload reduction, to post transplant patients. Our length of use ranges from 1 to 86 consecutive days on nesiritide. We have seen no major complications and are currently compiling the data for a retrospective safety review. Preliminary data shows that the mean and systolic systemic blood pressure, when recorded at 5 different data points (1st 24 hours, 2nd 24 hours, during maximum dose infusion, last 24 hours, and post infusion) is almost unchanged from the baseline pressure. Thus far, we have found no significant changes in serum sodium, creatinine, or urea nitrogen. We are also currently enrolling patients in several prospective studies to evaluate the effect of nesiritide in pediatric patients

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*"Nesiritide has been studied in over 1500 adult patients with decompensated CHF."*



 

with dilated cardiomyopathy admitted to the PICU, as well as in patients with single ventricle physiology. Our aim is to determine if nesiritide is useful in decreasing pulmonary arterial pressure (PAP), PCWP, RAP, SVR and PVR, as well as increasing cardiac index in this population. Other potential uses include Fontan patients with prolonged chest tube drainage and post transplant patients.

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# PEDIATRIC CARDIOLOGY TRAINING PROGRAM GUIDELINES – CURRENT STATUS

*By Tim C. McQuinn, MD*

### Introduction

A unique pediatric cardiology training guideline document is nearing completion. The guidelines were written by pediatric cardiologists "in the trenches" of pediatric cardiology fellowship training, including many of the readership of PCT. Development began in 1999 under the leadership of Rob Beekman, then President of the Society of Pediatric Cardiology Training Program Directors (SPCTPD). Task forces were created and documents written outlining guidelines for training in general pediatric cardiology, cardiac catheterization, cardiac intensive care, noninvasive imaging, research, adult congenital heart disease and electrophysiology training. The task forces were asked to formulate guidelines that would be mindful of previous publications, such as the American Society of Echocardiography's (ASE) guidelines for pediatric echocardiography training,(1) and consensus statements such as the 32nd Bethesda Conference "Care of the Adult With Congenital Heart Disease".(2) The goal was a final document that would be roughly parallel in design to COCATS - the Core Cardiology Training Statement for Adult Cardiovascular Medicine training.(3)

### Current Status

Through the efforts of Roberta Williams and David Sahn, in the fall of 2002 the American College of Cardiology (ACC) generously offered to sponsor finalization and publication of the SPCTPD guidelines. Rob Beekman and Thomas Graham were appointed Co-chairs of the writing committee and teams drawn primarily from the original SPCTPD task forces were appointed to participate in final revision of their portions of the document. All guidelines are now fully formulated or under final revision at the present time and it is expected that the document will be finished by spring of 2004. Publication in the Journal of the American College of Cardiology will represent a joint statement of the ACC, AHA, AAP and SPCTPD.

### Levels of Training

Although specific contents of the guidelines cannot be discussed prior to publication, I can make several generalizations. The guidelines will acknowledge two levels of expertise upon the completion of training. Level 1 training was defined as the level of training that a sound pediatric cardiology fellow should expect to achieve by the end of general training. 'Minimal' training, such as that sometimes advocated for fellows planning bench research careers, will not be described in the guidelines. Every task force was mandated to describe the content of Level 1 training, but not every task force defined the content of Level 2 training. Level 2 training was defined as training in the specialized skills necessary for an independent subspecialty career.

### Research Training

During the time that the guidelines were under development, the ABP removed its long-standing requirement for research training during subspecialty fellowships. The members of SPCTPD are uniformly in support of the importance of research training for pediatric cardiology training. The guidelines reflect this consensus by inclusion of a description of Level 1 and Level 2 research training.

### How to Define Enough?

The task forces often attempt to describe the number of months of exposure and/or the number of procedures or patient exposures generally needed to achieve specific skills. Every task Force was mindful that there is a diversity of training program structures. A basic distinction, for instance, exists between programs where fellows pursue highly defined activities for monthly rotations (e.g., cath rotation, echo rotation, etc) vs the training programs where fellows combine multiple activities such as rounding on inpatients, performing caths, and reading echos. Another important distinction exists between the programs with PCICUs run by the cardiology division and those programs where the cardiology role in ICU care is one of consultation. In attempting to define sufficient expo-

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sure for appropriate training, most guidelines therefore provide estimates of time commitment as well as numbers of specific procedures necessary to achieve proficiency.

**Summary and an Invitation**

I believe that the SPCTPD and the ACC have created a document that will be of great influence and practical assistance for pediatric cardiology training programs, but I do not believe that it is perfect or permanent. Despite the hard work invested to bring the guidelines to this point, our field is evolving

> ***"...the SPCTPD and the ACC have created a document that will be of great influence and practical assistance for pediatric cardiology training programs..."***

so rapidly that no description of appropriate training can remain static. We invite all readers of Pediatric Cardiology Today (PCT) to join SPCTPD and join the only organization dedicated to issues related to training in pediatric cardiology. One need not be a training program director to join; dues are only $25 per year for training program directors and $10 for each additional member from the same institution.

The next revision of the pediatric cardiology training guidelines is about to begin!

**References:**

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# HIGHLIGHTS FROM THE FIRST INTERNATIONAL CONFERENCE ON HEART FAILURE IN CHILDREN AND YOUNG ADULTS: FROM MOLECULAR MECHANISMS TO MEDICAL AND SURGICAL STRATEGIES - DECEMBER 3-6, 2003, THE INTERCONTINENTAL HOTEL IN HOUSTON, TEXAS

*By Anthony C. Chang, MD*

With increasing successes of palliative and reparative surgeries and catheter interventions, children with congenital heart disease are surviving but sometimes succumbing to progressive heart failure. Thus, heart failure in children and young adults has become a special area of clinical focus and the care for these patients demands a multidisciplinary approach involving cardiologists, cardiac surgeons, intensivists, anesthesiologists, and nursing. This four-day conference gathered the world's experts on heart failure, both in adult and pediatric cardiology and cardiac surgery with close to 500 attendees from 35 countries, representing more than 10 subspecialties. The entire conference started with a special welcome reception at the Museum of Fine Arts where the attendees enjoyed a private viewing of the special Museum of Modern Art collection from New York City (highlighted by the Starry Night by Vincent van Gogh).

Dr. James T. Willierson, an honorary chairman for this conference and editor of *Circulation*, started the scientific session with a plea for more research in pediatric heart failure and described his research experience with *bone marrow-derived stem cells* and their beneficial effects on the injured myocardium. Dr. Jeffrey Dreyer, Director of the Heart Failure Service at Texas Children's Hospital, then provided an overview for pediatric heart failure. In his overview, he alluded to the more current *neurohormonal activation* and *ventricular remodeling* models of adult heart failure and explored their similarities and differences in children with heart failure.

A basic science session of heart failure emphasized the importance of *dystrophin*, a protein that is the major link between the sarcomere and the sarcolemma in cardiac cells, and its major role in pathological mechanisms of ventricular dysfunction. Dr. Andrew Redington of Toronto Hospital for Sick Children presented his research on the use of pressure-volume loops via *conductance catheters* to delineate systolic and diastolic dysfunction as well as the force-frequency relationship of the failing heart. Dr. Douglas Mann, the editor of a recently-published textbook on heart failure in adults, emphasized that since heart failure cannot be defined in simple hemodynamic terms, objective assessment of ventricular performance should not focus on ejection fraction, but rather ventricular size and shape. Additional talks were provided on the assessment of heart failure by echocardiography, magnetic resonance imaging, and cardiac catheterization. Dr. James Huhta, well renowned for his pioneering work on echocardiographic assessment of the fetus, presented his work on the concept of a fetal *heart failure score*, utilizing umbilical vein and artery Doppler patterns as well as other noninvasive measurements. Dr. Steven Lipshultz, presently at University of Miami, presented his clinical experience with pediatric dilated cardiomyopathy, which included the fact that almost half of the children with dilated cardiomyopathy die or undergo transplantation within 5 years of diagnosis.

The surgical guest faculty discussed pertinent issues of heart failure patients from the surgical perspectives. Dr. Leonard Bailey, well known as the premiere heart transplantation surgeon in children, provided an update on pediatric heart transplantation, which numbers over 2,000 since 1982 and currently at about 350 per annum (with an actuarial survival of greater than 50 percent at 10 years). He also related an exciting option of *ABO-mismatched heart transplantation* in infant recipients as a means to improve organ procurement. He further predicted that there would be a referral shift away from neonates and infants and more toward children and young adults with failed ventricles in the near future.

***"'Failure is not an option…' ~ Gene Krantz, NASA flight director, during the imperiled flight of Apollo 13"***

Charles Fraser, Chief of Cardiac Surgery at Texas Children's Hospital, discussed surgical strategies for the ever- increasing challenge of the patient with a *failing ventricle*, including patients with congeni-



 

tally corrected transposition, transposition after Mustard or Senning repair, tetralogy of Fallot after repair, and with failing Fontan. Lastly, senior surgical associate from Boston Children's Hospital, Dr. John Mayer, elucidated the concept of *tissue engineering* and its use of progenitor cells for cardiovascular replacement of structures such as cardiac valves and small caliber arteries.

Dr. Jeffrey Towbin, Chief of Pediatric Cardiology at Texas Children's Hospital, provided the special lecture on *genetics of dilated cardiomyopathy* and heart failure. He detailed the underlying causes of dilated cardiomyopathy in children and the final common pathway. Important presentations on medical therapy and advances included pharmacological therapy in the ICU setting by Dr. Dan Penny of the Royal Children's Hospital in Melbourne, use of beta blockers and ACE inhibitors in the outpatient setting by Dr. Robert Shaddy of Salt Lake City, Utah, and a myriad of other relevant topics such as use of *B-type natriuretic peptide*, indications for resynchronization therapy, and the economic costs of heart failure in children.

The highlights of the meeting also included two-part mini-symposium on the state-of-the-art of acute and chronic mechanical support in heart failure patients. Dr. Denton Cooley chaired the part on pediatric mechanical support with several cardiac surgeons known for their work in this area, including Dr. William Gaynor (Children's Hospital of Philadelphia), Dr. Brian Duncan (Cleveland Clinic), and Dr. Tom Karl (University of California at San Francisco), all presented their valuable clinical experiences. The second part of this special mini-symposium highlighted the adult cardiac surgeons and their work on *ventricular assist devices*. Following an address by the venerable Dr. Michael DeBakey, Drs. George Noon, Bud Frazier, and Roland Hetzer, the most respected surgical authorities in the field of mechanical support in adult heart patients, all presented their work on various ventricular assist devices (the MicroMed DeBakey axial flow pump, the Jarvik pump, and the Berlin Heart ventricular assist device, respectively). This collective experience in adult patients will provide a valuable guideline for pediatric indications and use in the near future.

Much of the conference educational materials will be part of the textbook *Heart Failure in Children and Young Adults*, which is to be published by Elsevier and is due out in late 2004. In addition, the 50 selected abstracts (which included a wide variety of topics such as levosimendan, Doppler tissue and strain rate imaging, intra-aortic balloon pumping, etc) from the conference will be published by *Pediatric Cardiology* in early 2004. Lastly, the *Second International Conference on Heart Failure in Children and Young Adults* will be held in December of 2006. See you there!

*For comments to this article, send email to: JANAC@PediatricCardiologyToday.com*

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**Drug Information Association (DIA)**
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**The European Board for Accreditation in Cardiology (EBAC)**
www.ebac-cme.org

**European Institute of Healthcare (EIH)**
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**European Society of Cardiology (ESC)**
www.escardiocontent.org

**Federation of State Medical Boards (FSMB)**
www.fsmb.org

**Food, Drug and Law Institute (FDLI)**
www.fdli.org

**Heart Failure Society of America**
www.hfsa.org

**Health On the Net Foundation (HON)**
www.hon.ch

# TEXAS CHILDREN'S HOSPITAL DEDICATES LABS TO MULLINS

Major hospital facilities such as operating rooms and cardiac catheterization laboratories are usually "named for hospital donors." It is rare for a hospital-based physician to become so distinguished that a major medical center dedicates and names such a facility for the physician. Dr. "Chuck" Mullins is one of those rare distinguished physicians.

*The Charles E. Mullins, MD Cardiac Catheterization Laboratories* were dedicated to Dr. Mullins on December 6, 2003 at a Texas Children's Hospital ceremony in the hospital's Heart Center. Dozens of the heart center's alumni and spouses, current and retired center staff, Mrs. Ann McNamara, and three generations of the Mullins family attended the ceremony. Dr. Tom Vargo, a long-time colleague of Dr. Mullins, Dr. Ron Grifka, the current Director of the Mullins Catheterization Laboratories, and Dr. Jeff Tobin, the current Chief of Cardiology gave presentations honoring Dr. Mullins.

Dr. Vargo reviewed the history of cardiology at Texas Children's Hospital (TCH). He described Dr. Mullins as the "Father" of the pediatric cardiology program and Dr. Dan McNamara as the "Grandfather." According to Vargo, "Chuck and Dan" caused the Texas program "to blossom and bloom" into one of the world's premier pediatric cardiovascular programs.

Dr. Grifka calculated that as of December 5th, Mullins had performed 16,233 cardiac catheterizations at TCH and as a visiting cardiologist in some 306 institutions around the world. He noted that Dr. Mullins is widely recognized for his contributions to both diagnostic and interventional catheterization in children and in adults with congenital heart disease. Mullins is largely responsible for the current wide application of steerable catheterization techniques and trans-septal technology. Furthermore, he pioneered and developed the use of devices and stents, as applied to patent ductus arteriosus, septal defects and large vessel stenoses.


*Dr. "Chuck" Mullins and his wife Arlene standing in front of the Charles E. Mullins, MD plaque at the Texas Children's Hospital Cardiac Catheterization Laboratories*

***"Dr. Grifka calculated that as of December 5th, Mullins had performed 16,233 cardiac catheterizations at TCH and as a visiting cardiologist in some 306 institutions around the world."***

Grifka also noted that the impact of Dr. Mullins contributions has been amplified considerably by the large number of cardiologists he has trained – including 176 TCH pediatric cardiology fellows, 16 TCH 4th year interventional pediatric cardiology fellows, as well as hundreds of cardiologists around the world during visiting professorships. Dr. Mullins stands, in the company of only Drs. Rashkind and Lock, as one of the most important interventional pediatric cardiologists in the history of medicine.

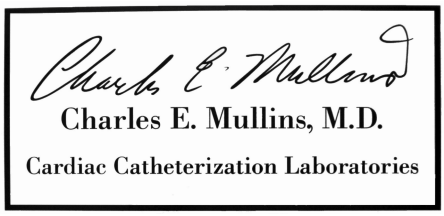
Mullins was born in Washington, DC. He graduated from Princeton University and George Washington University School of Medicine. He trained in pediatrics and cardiology at Walter Reed Army Medical Center. He served four years at Landstuhl Army Hospital in Germany and returned to Walter Reed for two additional years of military service. Dr. McNamara recruited Mullins to the faculty at TCH and Baylor



University Medical School in 1969. He rose to Professor and for the majority of his tenure was Director of the Cardiac Catheterization Laboratories at TCH.

For more than 30 years at TCH Dr. Mullins' priorities have been caring for patients, teaching and mentoring fellows, and developing new catheterization laboratory technology. In the process, he has compiled a massive resume including over 200 scientific articles, about 30 book chapters, and over




300 invited lectureships around the world. He has been honored by The American College of Cardiology, The American Academy of Pediatrics, The Society of Cardiac Angiography and Intervention and The Pediatric Interventional Cardiac Symposium for his professional accomplishments and for his teaching.

*For comments to this article, send email to: JANCM@PediatricCardiologyToday.com*

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# DOPPLER TISSUE IMAGING IN PEDIATRIC HEART DISEASE

*By Peter C. Frommelt, MD*

## Introduction

Echocardiography is well recognized as the primary non-invasive tool to assess myocardial systolic and diastolic function. In particular, quantitation of left ventricular ejection fraction based on volume analysis is the technique most commonly used to assess left ventricular systolic function. To assess left ventricular diastolic function, characterization of Doppler patterns of pulmonary venous and mitral inflow has been used. The utility of these techniques, however, is limited by the influence of other factors, including preload and afterload, heart rate, changes in intrathoracic pressure with respiration, and ventricular shape. Recent developments in ultrasound technology now allow display of instantaneous changes in myocardial velocities, which has been called Doppler tissue imaging (DTI). This new technique allows characterization of local myocardial velocities in both the radial and longitudinal planes, and this information can now be applied in the calculation of regional strain rate and strain values. DTI appears to have tremendous promise as a new method to assess both left and right ventricular function, and this review will describe some of the initial clinical applications in children and adults.

## Technical Aspects of Doppler tissue imaging

Doppler analysis of myocardial wall motion requires a modified filter and reduced gains to display the low-velocity, high-amplitude signals of the myocardium. Myocardial velocities may be recorded using either color Doppler or spectral pulsed Doppler signal processing. Color Doppler tissue imaging can be displayed either as a color-coded M-Mode or 2-dimensional data set. This technique measures mean velocities with both high temporal and spatial resolution in the axial direction. The color DTI signal is usually displayed superimposed on the underlying two-dimensional gray scale image (Figure 1) and is assessed in real time. Like the blood flow color Doppler convention where velocities are displayed as red to yellow towards the transducer and green to blue away from the transducer, myocardial motion is generally displayed in the same way.

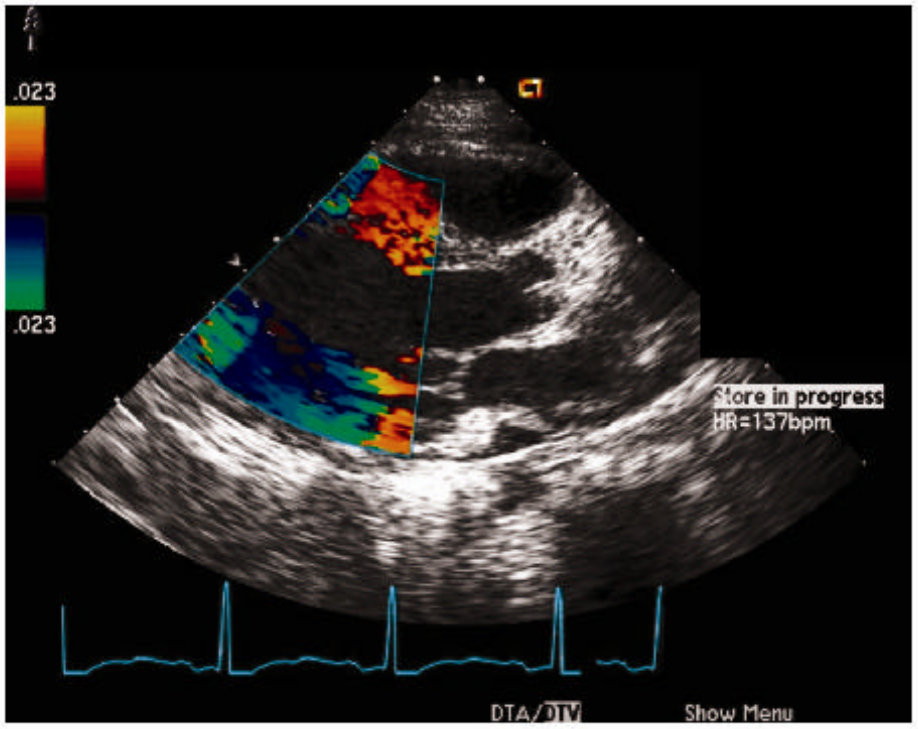


*Figure 1. Color Doppler tissue imaging of radial motion of the septal and posterior left ventricular walls from a parasternal long-axis window in a child with normal intracardiac anatomy. As can be seen by the color Nyquist scale, mean myocardial velocities are very low-velocity (Nyquist limit 2.3 cm/s), in contrast to blood flow velocities within the heart (where the color Doppler Nyquist is ideally 80-100 cm/s).*



 

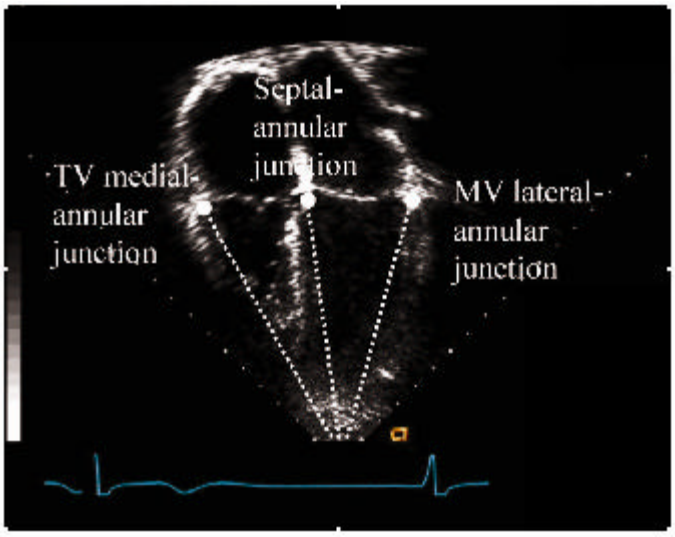


*Figure 2. Apical 4 chamber image of Doppler sample volume position for pulsed Doppler tissue imaging analysis of longitudinal mitral and tricuspid annular motion. Assessment of annular motion can be obtained from the mitral valve (MV) lateral-annular junction, the septal-annular junction, and the tricuspid valve (TV) medial-annular junction. Cursor alignment from the apical window places the Doppler beam in the plane of maximal longitudinal annular motion.*

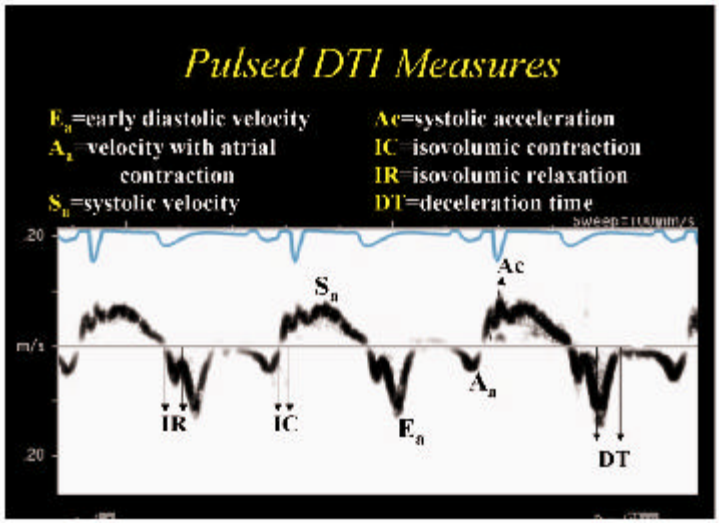


*Figure 3. Representative pulsed Doppler tissue imaging (DTI) recording of mitral annular motion in a child without heart disease. Systolic and diastolic velocity and time interval measures available are labeled. Note the low-velocity peaks in systole and early diastole (Doppler Nyquist limit 20 cm/s). Small, very low velocity waveforms are commonly seen during isovolumic relaxation (IR) and isovolumic contraction (IC) and likely represent translational changes in annular position.*

Although color DTI of 2-dimensional images provide only qualitative assessment of myocardial motion in real time, this has been found to be useful in identification of regional wall motion abnormalities related to ischemia or abnormal ventricular activation, and also has shown promise as a technique to identify accessory pathways in patients with Wolff-Parkinson-White syndrome.

For pulsed Doppler analysis, the sample volume is placed parallel to maximal radial (parasternal) or longitudinal (apical four chamber) motion. The majority of studies assessing myocardial motion using pulsed DTI have focused on longitudinal mitral and tricuspid annular motion, because the apical window allows parallel alignment of the Doppler cursor with the plane of maximal annular motion throughout the cardiac cycle (Figure 2). In order to best visualize the low-velocity spectral Doppler patterns, the Nyquist limit must be decreased to 10-20 cm/sec while using the lowest wall filter settings, and the dynamic range should be decreased to 30-35 dB with decreasing overall gains to minimize noise around the signal. Simultaneous display of an ECG recording is necessary to correlate timing of annular motion with cardiac electrical events, and the Doppler tracings are best displayed at a sweep speed of 100 mm/second to separate wave forms and assess temporal changes in myocardial wall motion. Since analysis of mitral and tricuspid annular motion has been the primary DTI technique utilized in pediatric cardiology, that will be the primary focus of this review.

***"Echocardiography is well recognized as the primary non-invasive tool to assess myocardial systolic and diastolic function."***

**DTI Assessment of Annular Motion in Pediatric Heart Disease**

Ventricular contraction and expansion occur along both the major and minor

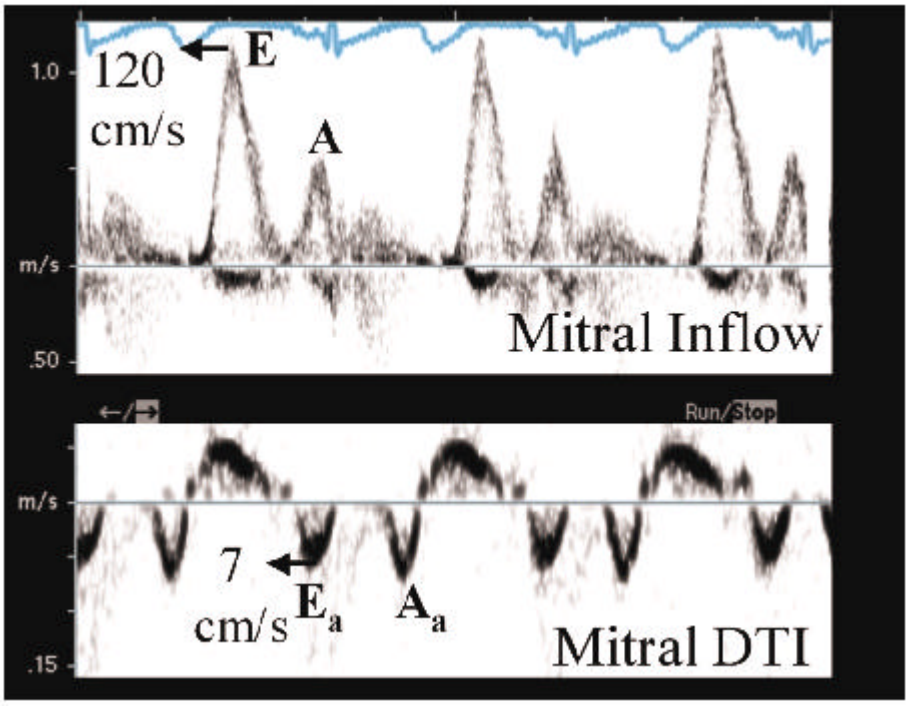


*Figure 4. Mitral inflow Doppler (top panel) and mitral annular pulsed DTI (bottom panel) recordings from a child with diastolic dysfunction and elevated filling pressures associated with chronic left ventricular hypertrophy. The mitral inflow tracing appears normal because the early diastolic filling (E) velocity has been "pseudonormalized" by elevated left atrial pressures. The mitral annular DTI tracing shows a significantly decreased early annular (Ea) velocity, however, reflecting abnormal diastolic relaxation that is unaffected by the elevation in filling pressure. Because the E wave velocity usually increases with increasing filling pressure while the Ea velocity remains decreased as diastolic disease progresses, the E/Ea ratio can be used as an index to identify elevated left ventricular diastolic pressure non-invasively. A ratio >15 has been correlated with mean left ventricular diastolic pressure >12 mmHg in adults (in this example E 120/Ea 7=17.1, which correlated with a left ventricular end-diastolic pressure of 15 mmHg).*

axes of the heart. Annular displacement of the atrioventricular valves towards the apex in systole reflects systolic longitudinal contraction of the heart and has been well correlated with ejection fraction. Annular displacement away from the apex in diastole reflects recoil or relaxation from the contracted state in early diastole and passive compliance of the ventricle during atrial systole. Since the cardiac apex is relatively fixed in position, it is an ideal window to assess annular motion. Pulsed DTI velocity profiles of annular motion provide both velocity and time interval information of myocardial motion at the annulus (Figure 3).

Normal values for both mitral and tricuspid annular motion profiles using DTI have been described for children and adults. This is important, as there has been recent recognition of several disease states where assessment of annular motion has been utilized to better understand myocardial dysfunction in children. These studies have focused on pathologic left ventricular hypertrophy, cardiomyopathies, graft function following heart transplantation, and tetralogy of Fallot after surgical repair.

In children with pathologic left ventricle hypertrophy, significant septal and lateral mitral annular DTI changes have been identified compared to normal children. Pathologic left ventricular hypertrophy results in a lower early diastolic annular velocity (Ea 8.2 vs. 12.4 cm/s), decreased Ea/Aa ratio (1.6 vs. 2.8), and marked prolongation in the time from end-systolic annular motion to the peak early diastolic annular motion (151 vs. 107 ms). These changes in annular motion have been correlated with a shift in transmitral filling from early to late diastole with prolongation in isovolumic relaxation time; all these findings appear to reflect abnormal relaxation in the pathologically hypertrophied ventricle.

***"Recent developments in ultrasound technology now allow display of instantaneous changes in myocardial velocities, which has been called Doppler tissue imaging (DTI)."***



 

DTI patterns of annular motion have been utilized to differentiate pathologic hypertrophy from the physiologic hypertrophy frequently seen in competitive high school and college athletes.

***"Application of this technique in patients with systemic right ventricles after surgical palliation for congenital heart disease and in those with single ventricle physiology may provide additional insight and quantitative analysis of myocardial function in these challenging patient groups."***

The "athletic" heart has normal early diastolic annular peak velocities and isovolumic relaxation as assessed by mitral annular DTI compared to those with pathologic hypertrophy. This decrease in Ea velocity with abnormal relaxation appears to be independent of preload and changes in left atrial pressure, in contrast to mitral inflow velocities. Since abnormal relaxation can be masked on the mitral inflow Doppler by elevated filling pressure (resulting in the "pseudonormal" pattern), identification of significantly lower Ea velocities from the DTI tracing may provide a more sensitive indicator of diastolic dysfunction and has been used to predict elevation in left ventricular filling pressure (Figure 4).

In children with cardiomyopathies, DTI assessment of annular motion has shown significant promise in characterizing the disease state. In patients with hypertrophic cardiomyopathy, annular DTI patterns have identified hypertrophic cardiomyopathy in the absence of pathologic hypertrophic changes, suggesting that this technique may identify a genetic predilection for the disease before phenotypic expression can be identified by 2-dimensional imaging. DTI patterns in patients with hypertrophic cardiomyopathy can also predict elevations in left ventricular filling pressure using the E/Ea ratio described above. In addition, DTI patterns of annular motion have been utilized to predict functional class and exercise capacity in adults with this disease. Finally, these patterns have identified asynchronous diastolic function in children with hypertrophic cardiomyopathy (Figure 5) and have been used to assess the benefit of calcium channel blocker therapy in improving diastolic function. In adults with dilated cardiomyopathy, pulsed DTI has been useful in separating those with mild congestive heart failure from those with more severe heart failure. In patients with restrictive cardiomyopathy, DTI annular patterns have been useful in differentiating myocardial restriction (where early diastolic annular velocities are abnormally low and reflect abnormal relaxation) from those with constrictive pericardial disease, where diastolic myocardial properties are well preserved.

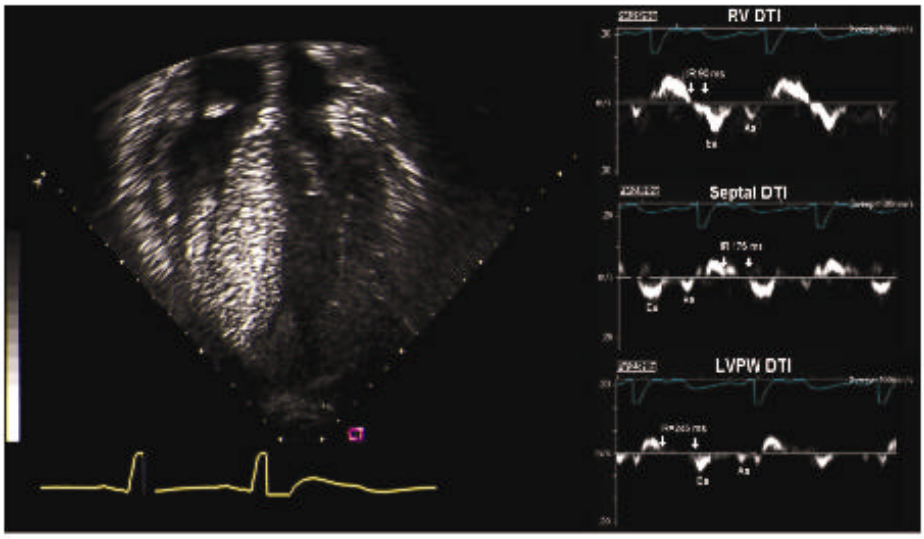


*Figure 5. Apical 4 chamber image and pulsed DTI recordings from the left ventricular posterior wall (LVPW), ventricular septum, and right ventricular (RV) free wall in a child with hypertrophic cardiomyopathy. Although the septum appears most affected by 2-dimensional imaging, diastolic dysfunction is identified by DTI in all 3 areas interrogated with prolonged isovolumic relaxation (IR) and decreased early diastolic (Ea) velocities compared to normals. The asynchronous diastolic relaxation properties of different segments of the myocardium in this disease are also evident by the variable IR (90 ms in the RV compared to 246 ms in the LVPW) and variable Ea velocities found at each site.*

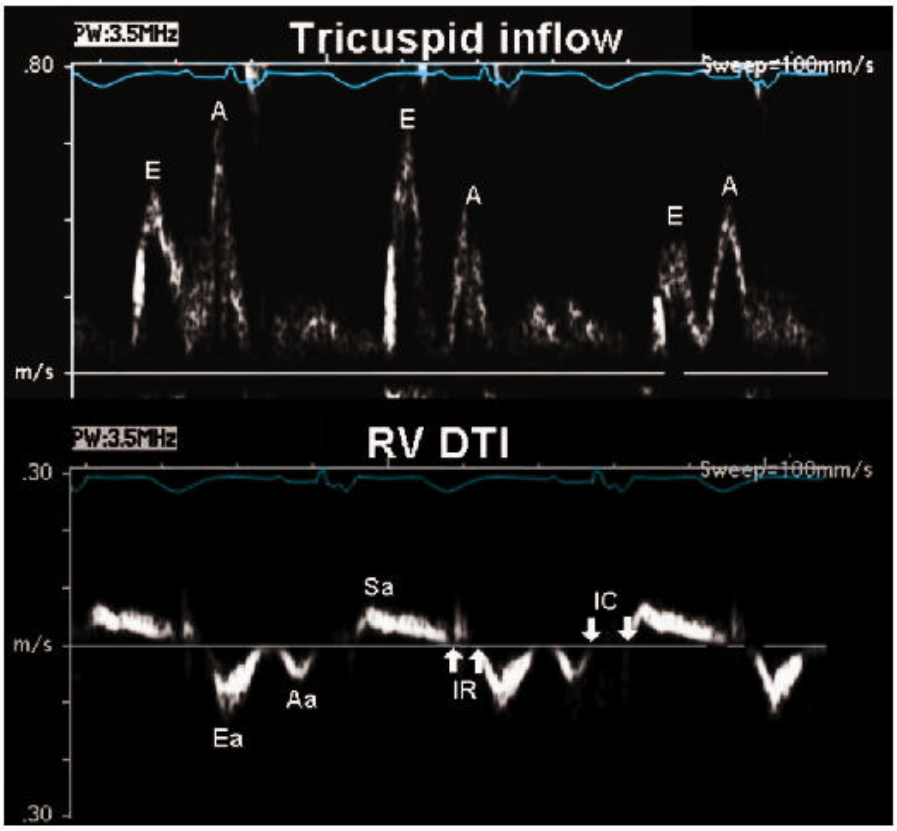


*Figure 6. Tricuspid inflow Doppler (top panel) and tricuspid annular pulsed DTI (bottom panel) recordings from a child with tetralogy of Fallot after repair with severe pulmonary insufficiency. The tricuspid inflow Doppler pattern is difficult to interpret because of marked variations in velocities with changes in respiration. In contrast, the DTI tracing is stable throughout the respiratory cycle, reflecting the preload independence of annular motion. In addition, both systolic indexes of annular motion, such as peak systolic velocity (Sa) and isovolumic contraction (IC), and diastolic indexes of annular motion, such as early diastolic velocity (Ea), diastolic velocity with atrial contraction (Aa), and isovolumic relaxation (IR), are measurable from the DTI trace.*

In patients after cardiac transplantation, assessment of annular motion using DTI has been a potentially sensitive technique in identifying rejection. Rejection of the graft appears to correlate with Ea velocities, as patients with no rejection had an Ea velocity of 21 cm/s compared to 14 cm/s for those with moderate to severe rejection by myocardial biopsy. Importantly, this technique appears most useful when patients are followed serially; rejection was best correlated with a decrease in the Ea velocity of greater than 20% from baseline in the same patient. In addition, there was no correlation between peak systolic annular velocity and rejection.

In patients with tetralogy of Fallot after complete repair, tricuspid annular and right ventricular DTI patterns have identified delayed right ventricular relaxation, restrictive right ventricular filling, and abnormal right ventricular systolic function. These changes have been correlated with pathologic EKG changes, suggesting that DTI patterns may also be predictive of higher-risk outcomes late after surgery. This technique holds considerable promise in the assessment of right ventricular function, as current echo methods have significant limitations. No adequate right ventricular geometric model has been developed to allow simple volume analysis or calculation of ejection fraction using echocardiography, and Doppler inflow patterns of right ventricular filling appear to vary more with changes in intrathoracic pressure and systemic venous return rather than to alterations in the intrinsic diastolic properties of the ventricle (Figure 6). DTI assessment provides preload-independent systolic and diastolic indexes of function. Application of this technique in patients with systemic right ventricles after surgical palliation for congenital heart disease and in those with single ventricle physiology may provide additional insight and quantitative analysis of myocardial function in these challenging patient groups.

***"These initial studies suggest the potential application of this technique in many forms of pediatric heart disease."***



 

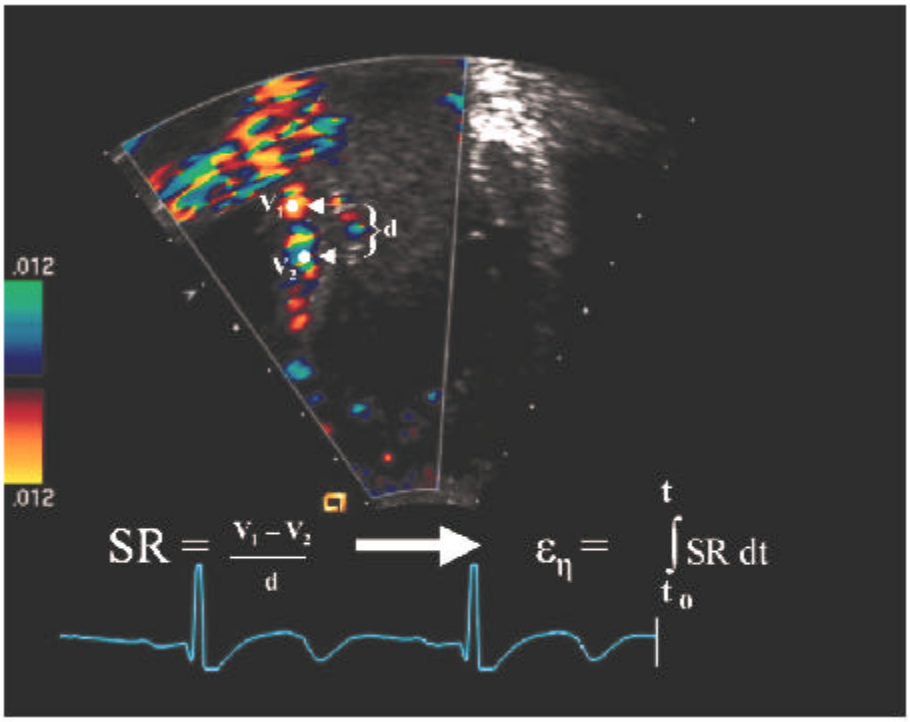


*Figure 7. Apical 4 chamber image with color Doppler tissue velocity map superimposed on the 2-dimensional image along the ventricular septum. The calculations of regional strain rate (SR) and natural strain (en) are described. Myocardial SR is the difference of 2 velocities (V1 – V2) divided by the distance (d) between the 2 points where the velocity information was extracted. Natural e is measured by integrating SR over time.*

**Strain Rate/Strain Imaging**

Although myocardial velocity profiles of segmental motion has become a useful technique in the assessment of heart disease, a more accurate index of myocardial function would quantitate regional myocardial strain rates and strain. These indexes of myocardial deformation more accurately reflect regional function when compared to myocardial velocities, as they are independent of overall heart motion. Regional strain rate corresponds to the rate of deformation of a myocardial region of interest. Strain rate curves are calculated from local velocity data, where the strain rate is the difference of two velocities in a segment of interest divided by the distance between those two velocity points (Figure 7). Strain is calculated by integrating strain rate over time and is expressed as a percentage.

Normal values for systolic and diastolic strain rate and strain from all segments of the left and right ventricle have been described in both adults and children. Strain rate and strain imaging appear to be an important new method for the quantitation of both left ventricular and right ventricular function. Initial studies in children after the Senning operation show reduced longitudinal systolic and diastolic deformation of the systemic right ventricle when compared to right ventricles in the pulmonary circulation. There also appears to be a strong correlation between local systolic strain of the systemic right ventricular free wall and calculated right ventricular ejection fraction as measured by MRI. In addition, case reports of regional abnormalities in strain rate and strain indexes in an infant following repair of anomalous origin of the left coronary artery from the pulmonary artery and in nonobstructive hypertrophic cardiomyopathy have been published. These initial studies suggest the potential application of this technique in many forms of pediatric heart disease.

*For comments to this article, send email to: JANPF@PediatricCardiologyToday.com*

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