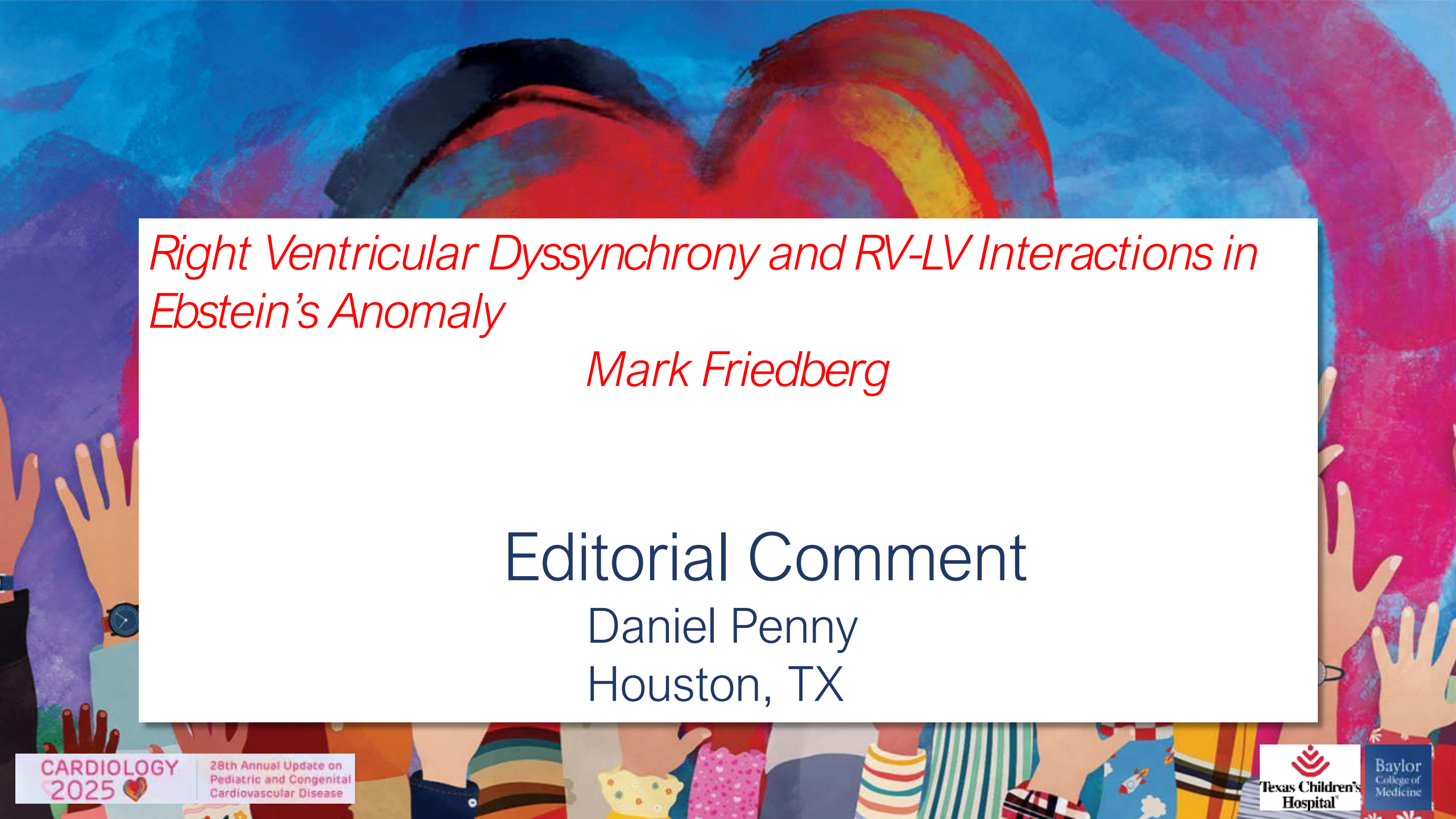


Right Ventricular Dyssynchrony and RV-LV Interactions in Ebstein's Anomaly

Mark Friedberg

Editorial Comment

Daniel Penny
Houston, TX

CARDIOLOGY 2025
28th Annual Update on Pediatric and Congenital Cardiovascular Disease

Texas Children's Hospital
Baylor College of Medicine

Function of The Cardiac Myocyte

MBoC PERSPECTIVE ON CELL BIOLOGY AND HUMAN HEALTH

Biology of the cardiac myocyte in heart disease

Angela K. Peter, Maureen A. Bjerke, and Leslie A. Leinwand*
BioFrontiers Institute, Department of Molecular, Cellular and Developmental Biology, University of Colorado, Boulder, CO 80309

ABSTRACT Cardiac hypertrophy is a major risk factor for heart failure, and it has been shown that this increase in size occurs at the level of the cardiac myocyte. Cardiac myocyte model systems have been developed to study this process. Here we focus on cell culture tools, including primary cells, immortalized cell lines, human stem cells, and their morphological and molecular responses to pathological stimuli. For each cell type, we discuss commonly used methods for inducing hypertrophy, markers of pathological hypertrophy, advantages for each model, and disadvantages to using a particular cell type over other in vitro model systems. Where applicable, we discuss how each system is used to model human disease and how these models may be applicable to current drug therapeutic strategies. Finally, we discuss the increasing use of biomaterials to mimic healthy and diseased hearts and how these matrices can contribute to in vitro model systems of cardiac cell biology.

Monitoring Editor
David G. Drubin
University of California, Berkeley

Received: Apr 27, 2016
Revised: May 20, 2016
Accepted: May 23, 2016

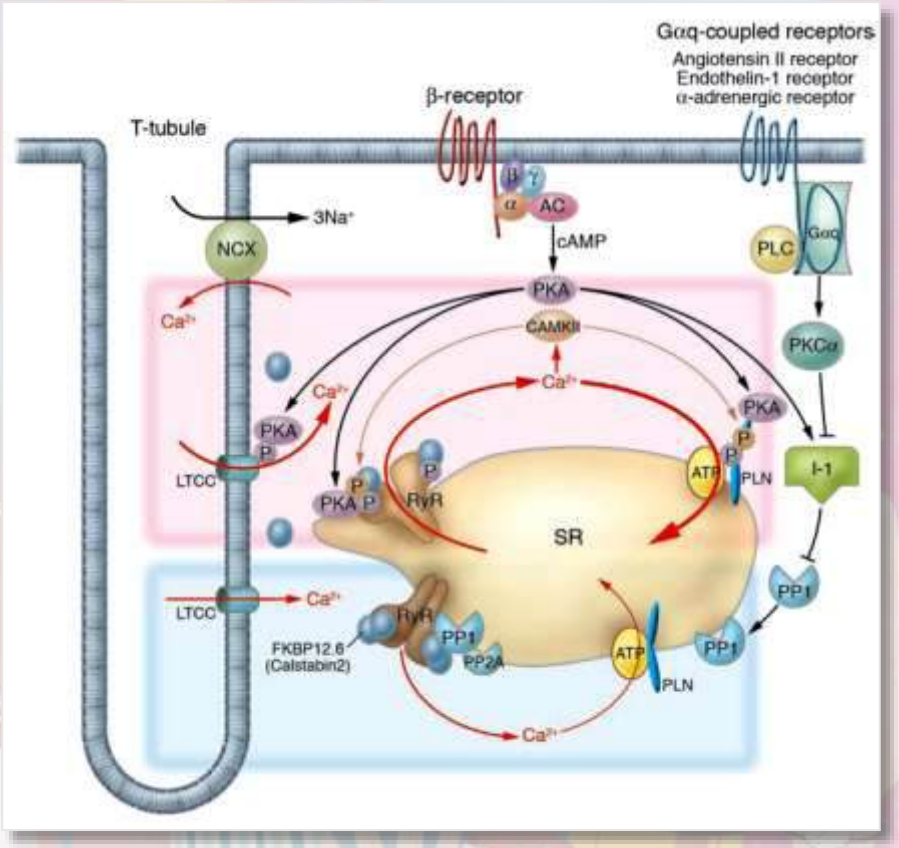
INTRODUCTION

In this review, we discuss the cell biology of heart disease, using the cardiac myocyte as our focus. Although there are many cell types in the heart (myocytes, endothelial cells, fibroblasts, vascular smooth muscle cells), and each cell type contributes to cardiac function, we discuss the contractile myocytes. Myocytes constitute the majority of the heart by mass and have been shown to be major contributors to contractile dysfunction. We discuss various approaches that have been used to study myocyte cell biology in the setting of heart disease and cover recent advances.

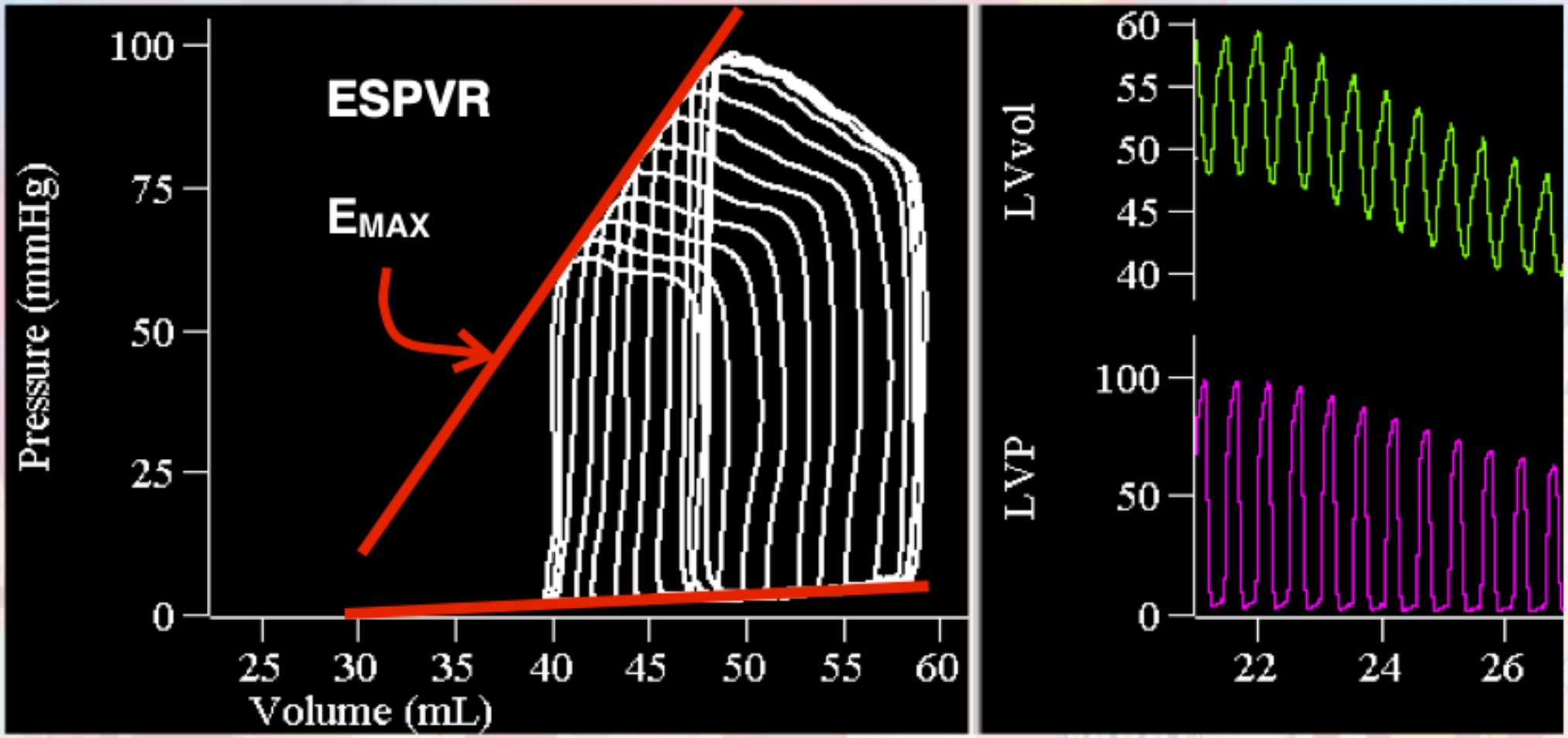
For more than three decades, rodent models have been used to study heart disease with many different etiologies; despite divergent causes, cardiac hypertrophy is frequently a common disease indicator (Curtis *et al.*, 1987; Rockman *et al.*, 1991). In fact, pathological cardiac hypertrophy is a strong prognostic indicator of human morbidity and mortality (Kono *et al.*, 2009; Takasaki *et al.*, 2012; Shenasa *et al.*, 2015). It should be mentioned that there is also a type of cardiac hypertrophy that is physiological and caused by stimuli such as exercise and pregnancy, but this type of hypertrophy is distinct and will not be discussed here. Cardiac hypertrophy is largely the result of cardiac myocyte enlargement, and this process can be recapitulated in isolated myocytes in culture by treatment with a number of small molecules and growth factors. Myocytes either contract spontaneously or can be paced to contract and their contractile properties studied. Primary cardiomyocytes are terminally differentiated cells and are difficult to transfect (Naqvi *et al.*, 2009). Therefore some effort has been put into developing permanent cell lines, but these lines suffer from their relevance to bona fide cardiac myocytes (see later discussion). Purification of cardiomyocytes greatly reduces or eliminates other cell types in the heart, including endothelial cells and fibroblasts, making it possible to attribute findings to the cardiac myocytes rather than interactions with other cell types (Díaz and Wilson, 2006). Studying cardiomyocytes offers many inherent advantages over whole-heart models, allowing precise control of experimental conditions, including extracellular matrices, exogenous growth factors, oxygen levels, and electrical stimulation.

In addition to animal models and primary cardiac myocytes from experimental animal models, much recent work has been done to develop human cardiomyocyte model systems. These include differentiation of human embryonic stem cells (ESCs) and human induced pluripotent stem cells (iPSCs) into cardiomyocytes. These models are discussed here, and although they may ultimately be the best model for studying human cardiomyocytes, considerable research is still needed to direct these cells to a fully differentiated cardiomyocyte phenotype.

DOI: 10.1091/mbc.E16-01-0038
*Address correspondence to: Leslie A. Leinwand (leslie.leinwand@colorado.edu).
Abbreviations used: α-SMA, alpha-skeletal muscle actin; AMVM, adult mouse ventricular myocyte; ANF, atrial natriuretic factor; Ang II, angiotensin II; ARVM, adult rat ventricular myocyte; β-MHC, beta-myosin heavy chain; BNP, brain natriuretic peptide; cAMP, adenosine 3,5-cyclic monophosphate; DCM, dilated cardiomyopathy; ESC, embryonic stem cell; ET-1, endothelin-1; HCM, hypertrophic cardiomyopathy; iPSC, induced pluripotent stem cell; ISO, isoproterenol; MLP, muscle LIM protein; NE, norepinephrine; NMVM, neonatal mouse ventricular myocyte; NRVM, neonatal rat ventricular myocyte; PE, phenylephrine; PMA, phorbol 12-myristate 12-acetate.

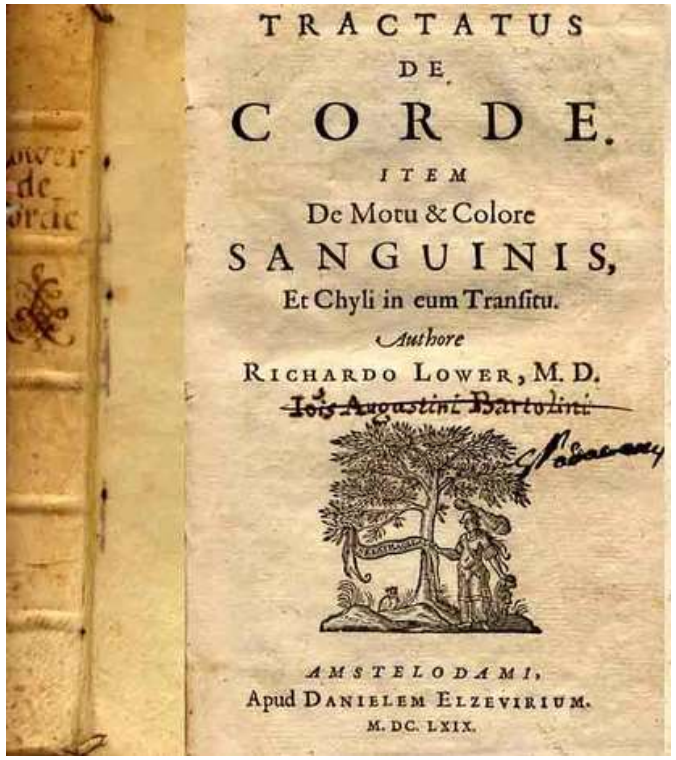


Ventricular Chamber Elastance – Suga et al.



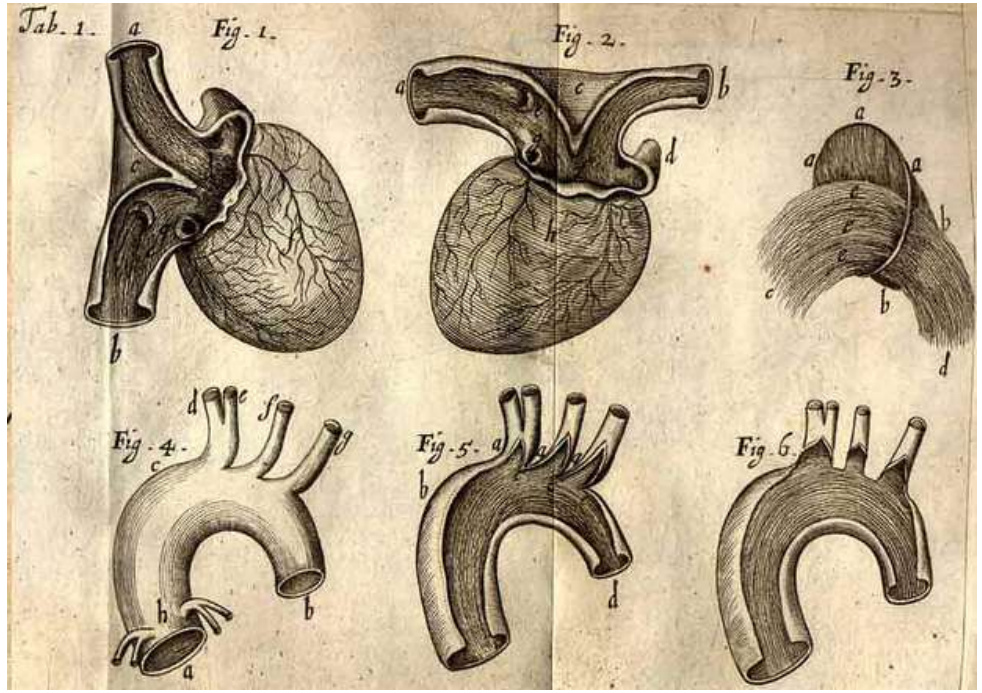
Not Just Shortening of The Myocyte

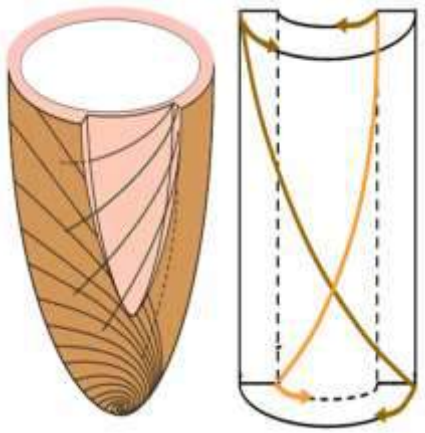
Twisting and Untwisting


TRACTATUS
DE
CORDE.
ITEM
De Motu & Colore
SANGUINIS,
Et Chyli in eum Transitu.
Authore
RICHARDO LOWER, M. D.
Amstelodami,
Apud Danielem Elzevirium.
M. DC. LXIX.

"… the wringing of a linen cloth to squeeze out the water"

Lower 1669





Not Just Shortening of The Myocyte

Incoordination

456

Br Heart J 1991;66:456-9

Angiographic demonstration of incoordinate motion of the ventricular wall after the Fontan operation

Daniel J Penny, Andrew N Redington

Abstract

***Objective*—To study regional wall motion of the systemic ventricle in patients after the Fontan operation.**

***Design and patients*—Systemic ventricular angiograms of 15 patients after the Fontan operation and of 11 unoperated patients with a univentricular atrioventricular connection were digitised frame by frame. Strict criteria for abnormal wall motion were used so that minor abnormalities were not considered.**

***Results*—Incoordinate contraction of the ventricular wall was found in five of the 11 patients before and in four of the 15 patients after the Fontan operation (NS). Only three of the 11 patients before the Fontan operation, showed incoordination of ventricular relaxation, but incoordinate relaxation was seen in 12 of the 15 patients after operation ($p < 0.01$).**

***Conclusions*—Whereas incoordination of ventricular contraction was common in patients with a univentricular atrioventricular connection, before or after the Fontan operation, incoordinate relaxation of the ventricular wall was a common consequence of the Fontan operation and was rare in patients before operation.**

The assessment of systemic ventricular function in patients after the Fontan operation[1] has principally relied on the assessment of global systolic pump activity.[2-5] The indices used have been based on the extrapolation of the contractile properties of single myocardial fibres to the intact heart,[6] and it has been assumed that any derangement in such indices might reflect abnormalities of ventricular "contractility". The use of these indices, however, neglects potentially important regional abnormalities of timing and function, which may have important implications for ventricular pressure development,[7] relaxation,[7,8] and diastolic filling,[9] even when the functional properties of the individual myofibrils are normal. It follows therefore that any abnormalities in measured indices of global ventricular contraction or filling cannot be ascribed to abnormal ventricular "contractility" or "compliance" unless abnormalities of regional function have been excluded.

It is thus timely to extend the assessment of systemic ventricular function in patients after the Fontan operation beyond the analysis of global pump function and to include the study of regional variation in ventricular wall movement. This is particularly pertinent to those geometrically unusual ventricles that are subjected to profound changes in loading conditions at the time of operation.

We have previously described the presence of abnormal intraventricular Doppler flow in patients after the Fontan operation,[1] and have proposed that the presence of this intraventricular flow, as in other patients with left ventricular disease,[7,10] may reflect the presence of regional abnormalities of ventricular function. A direct assessment of regional ventricular function, however, has not been performed in this patient group. In this study we have attempted such an assessment by frame by frame analysis of ventricular angiograms before and after the Fontan operation in patients with a univentricular atrioventricular connection.

Methods

PATIENTS

We studied 26 patients. Fifteen patients with a median age of 104 (range 43–198) months were studied at a median interval of 17 (5–54) months after the Fontan operation. Of these, nine had tricuspid atresia with a concordant ventriculoarterial connection. Five patients had double inlet left ventricle (with a discordant ventriculoarterial connection in three, a concordant ventriculoarterial connection in one, and pulmonary atresia in one). One patient had pulmonary atresia with an intact ventricular septum. Atriopulmonary anastomosis had been performed in 12, and in two the rudimentary right ventricle was included in the anastomosis, with closure of the ventricular septal defect. One patient with double inlet left ventricle and a restrictive ventricular septal defect underwent the Damus-Kaye-Stansel procedure at the time of the Fontan operation. At the time of study all patients were in functional class I or II and none had evidence of significant atrioventricular valve regurgitation on angiography. One patient had a restrictive ventricular septal defect, which was subsequently enlarged.

Eleven patients with a univentricular atrioventricular connection were studied before the Fontan operation at a median age of 51 (35–160) months. Of these, six had tricuspid atresia (with a concordant ventriculoarterial connection in five and a discordant

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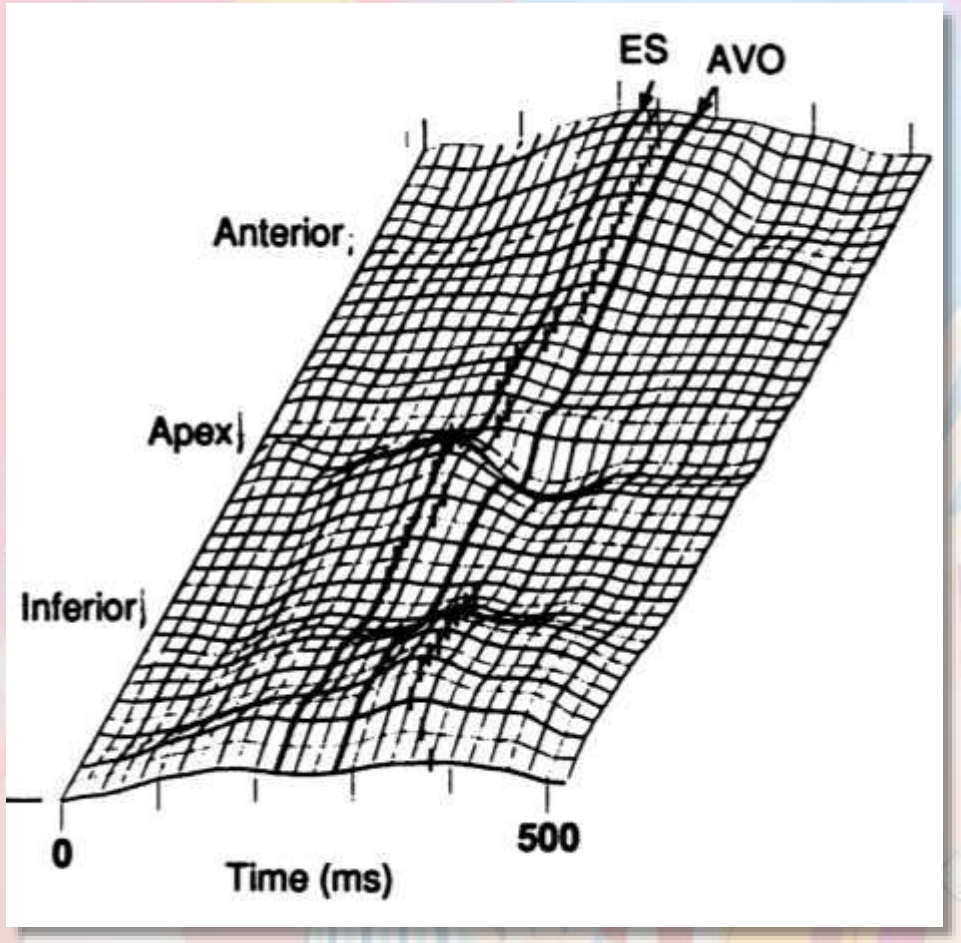
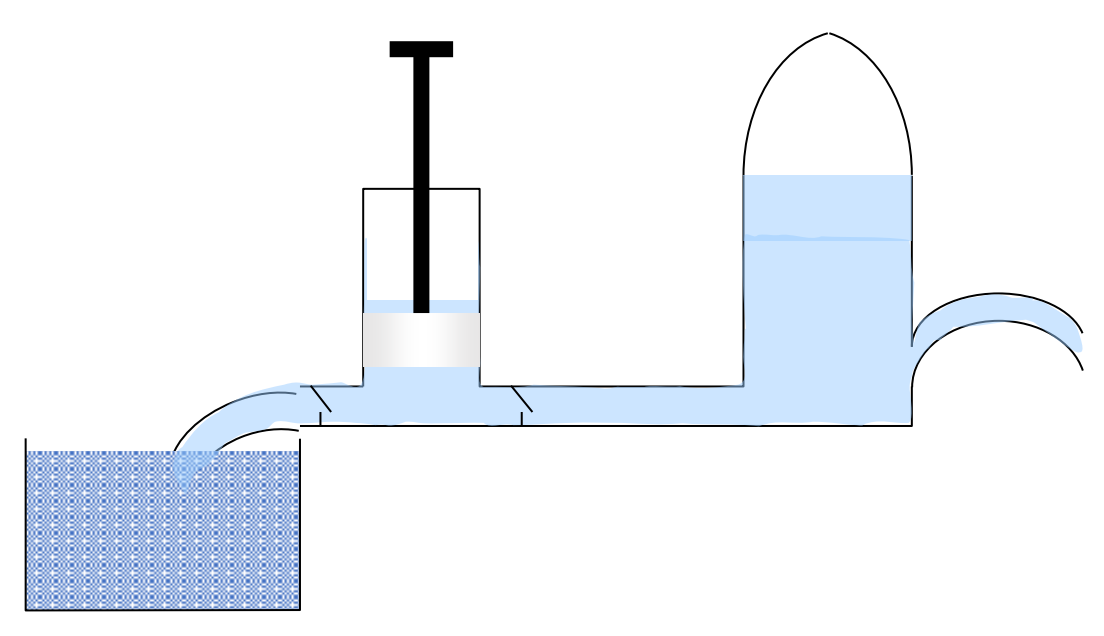
Accepted for publication 1 August 1991



Ventriculovascular Coupling



Pressure-Volume Domain

Arterial Elastance (EA)

Frequency Domain

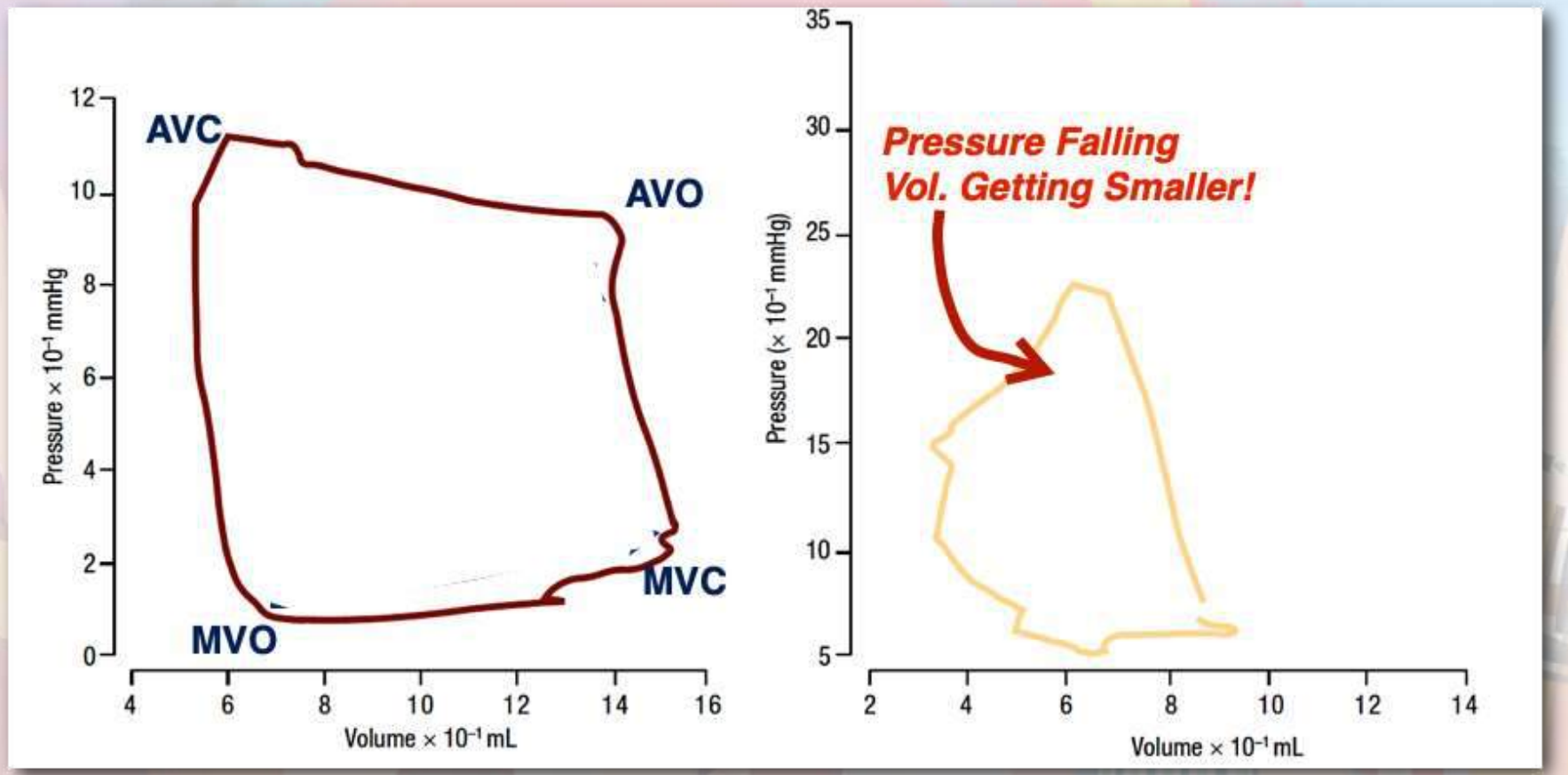
Characteristic Impedance

Fast frequency transformation

Time-Series Domain

Method of Characteristics (dPdU)

The Left and Right Ventricles are Different



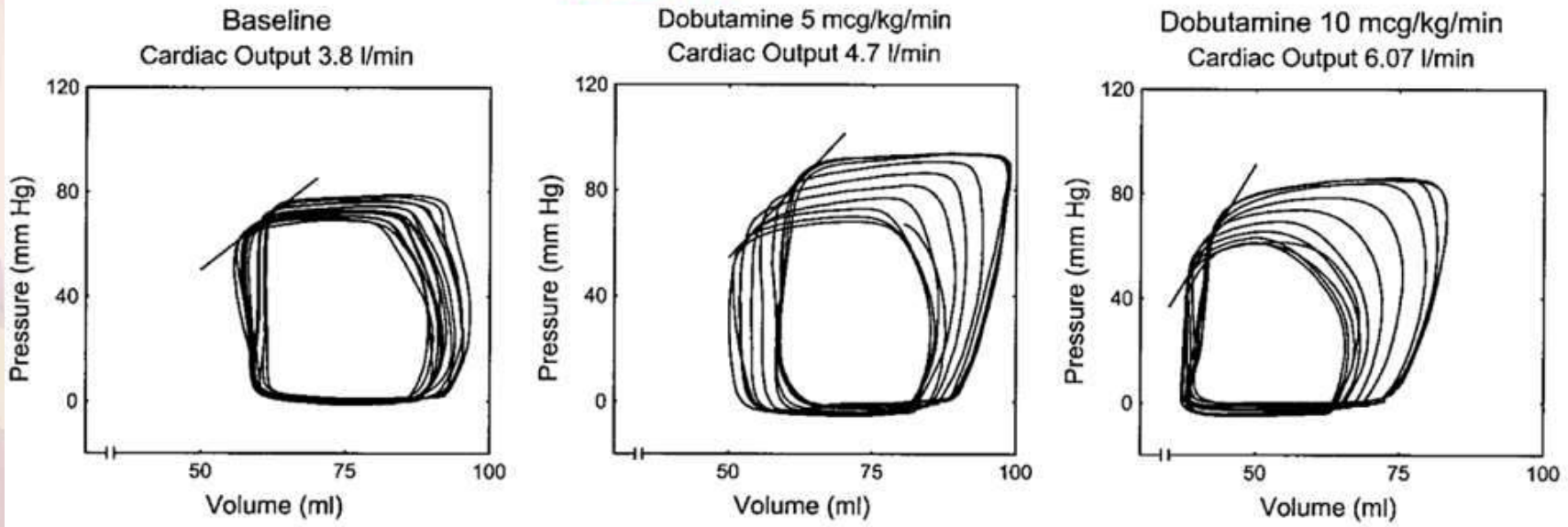
Modified From Greyson CR Rev Esp Cardiol 2010

Right Ventricular Function and Load

Failure of Stroke Volume Augmentation During Exercise and Dobutamine Stress Is Unrelated to Load-Independent Indexes of Right Ventricular Performance After the Mustard Operation

Graham P. Derrick, BMedSci, BM, BS, MRCP; Indra Narang, BMedSci, BM, BS, MRCP; Paul A. White, PhD; Andrea Kelleher, BM, BS, FRCA; Andrew Bush, MD, FRCP; Daniel J. Penny, MD, MRCP; Andrew N. Redington, MD, FRCP

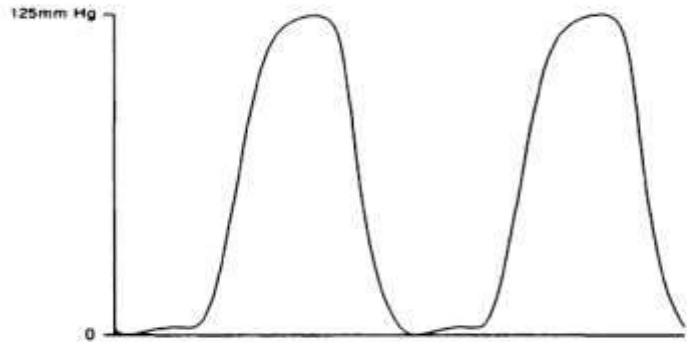
RIGHT VENTRICULAR PRESSURE- VOLUME LOOP AFTER MUSTARD OPERATION



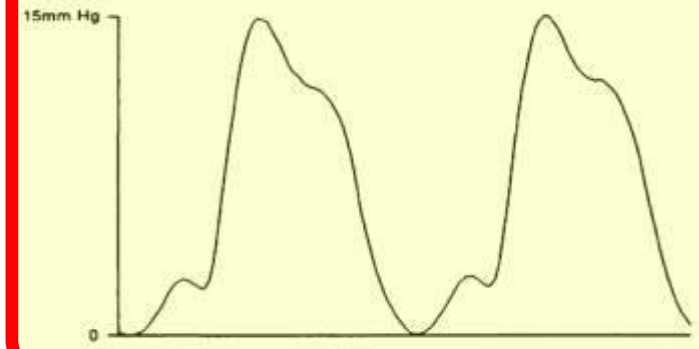
Ventricular Interdependence

Right-Left Ventricular Interactions – Damiano et al.

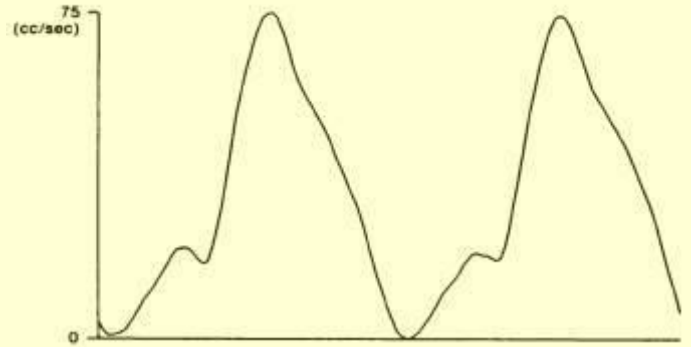
Left Component of LV Pressure



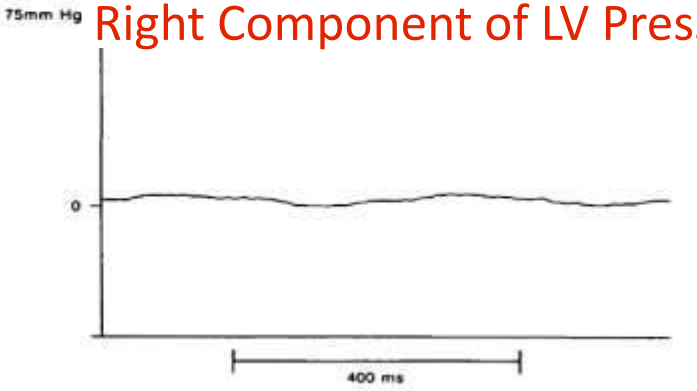
Left Component of RV Pressure



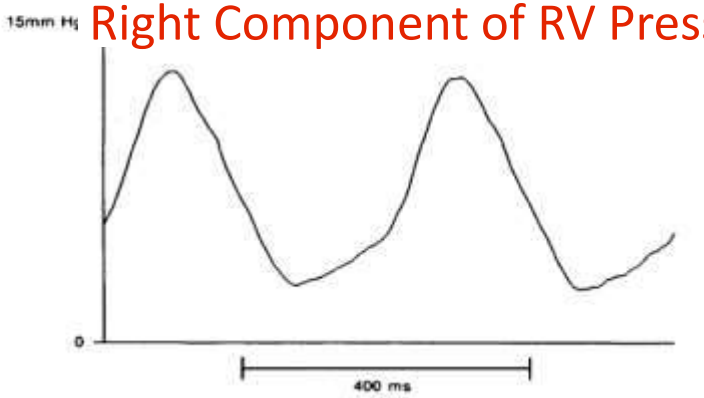
Left Component of PA Flow



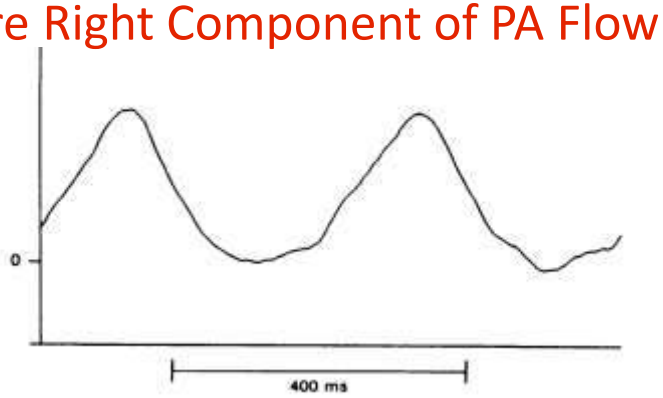
Right Component of LV Pressure

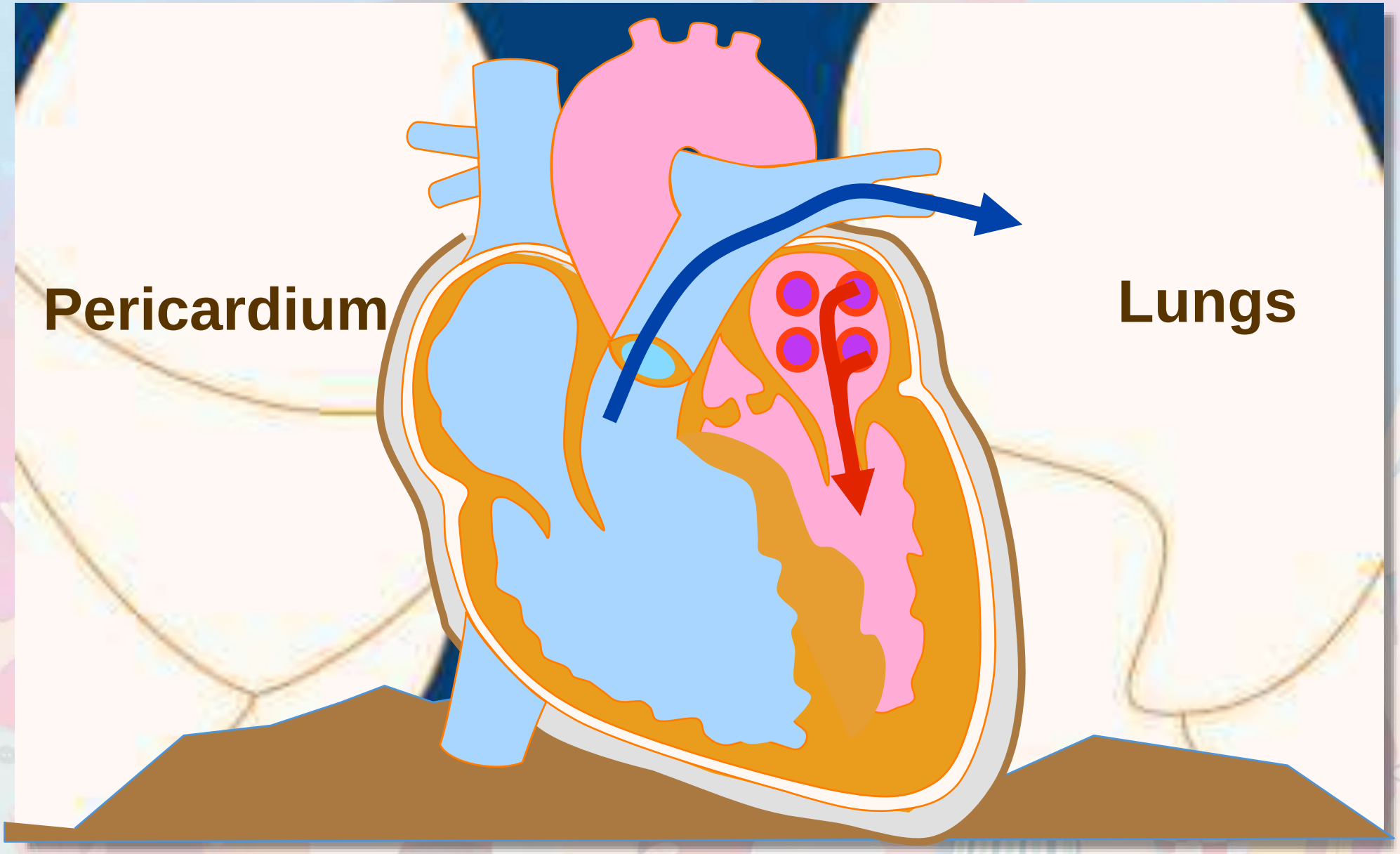


Right Component of RV Pressure



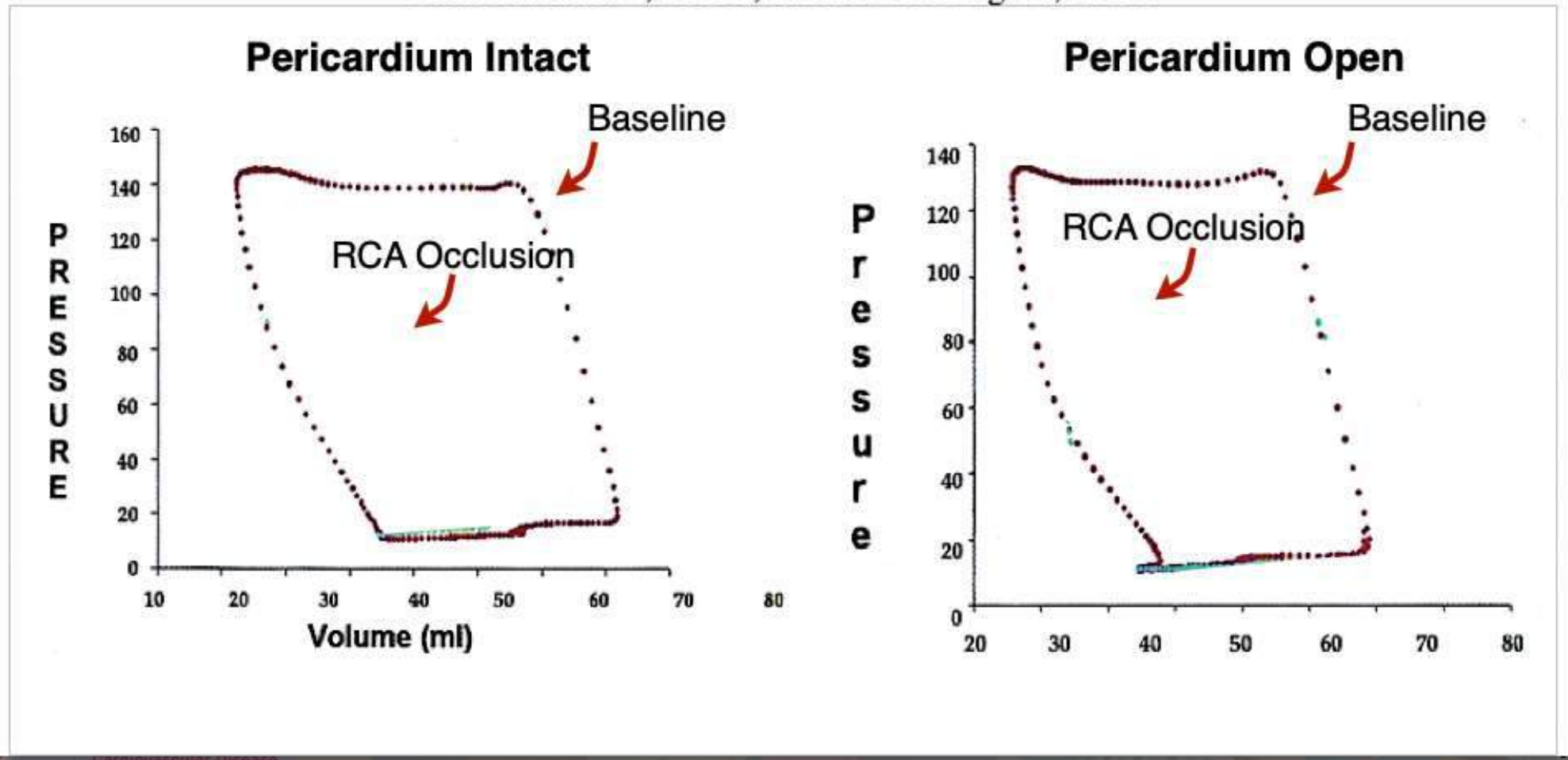
Right Component of PA Flow



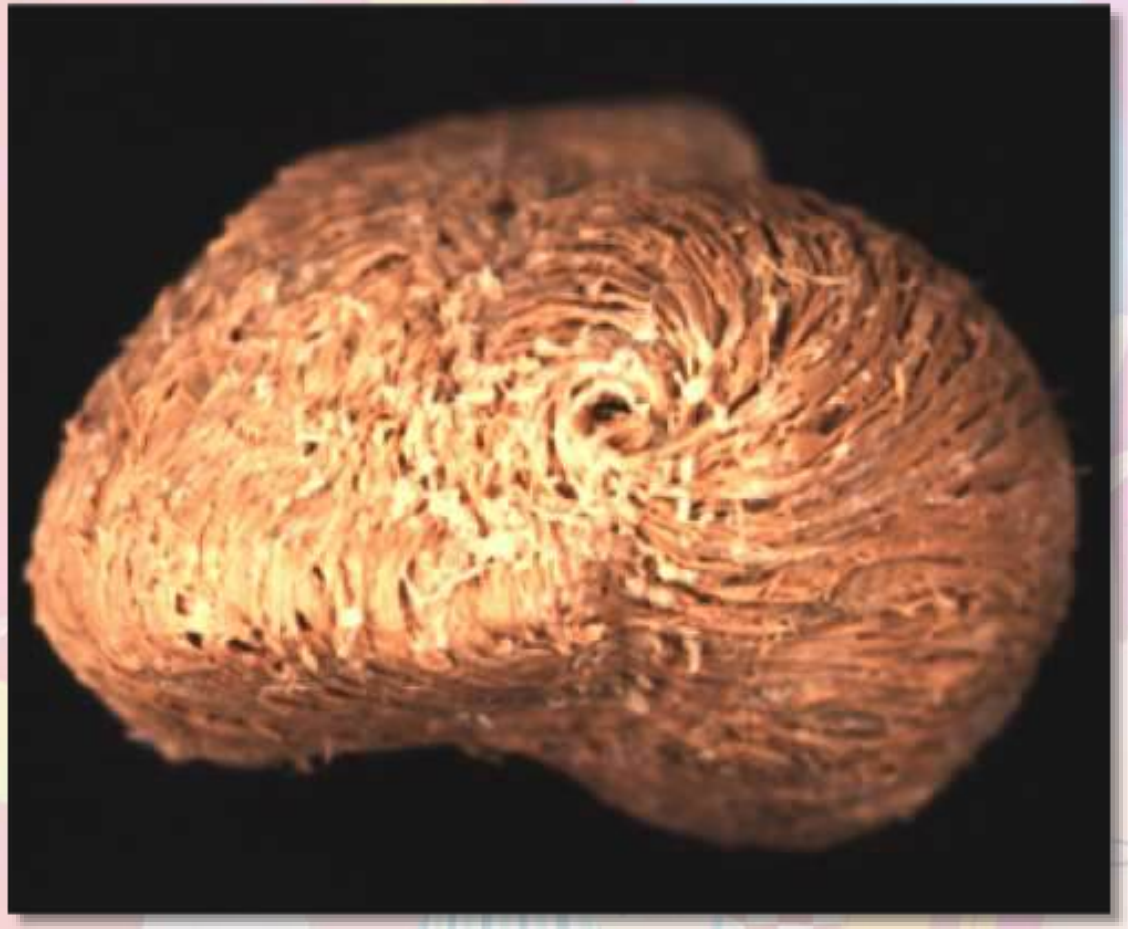

Pericardium
Lungs

Acute Right Ventricular Dilatation in Response to Ischemia Significantly Impairs Left Ventricular Systolic Performance

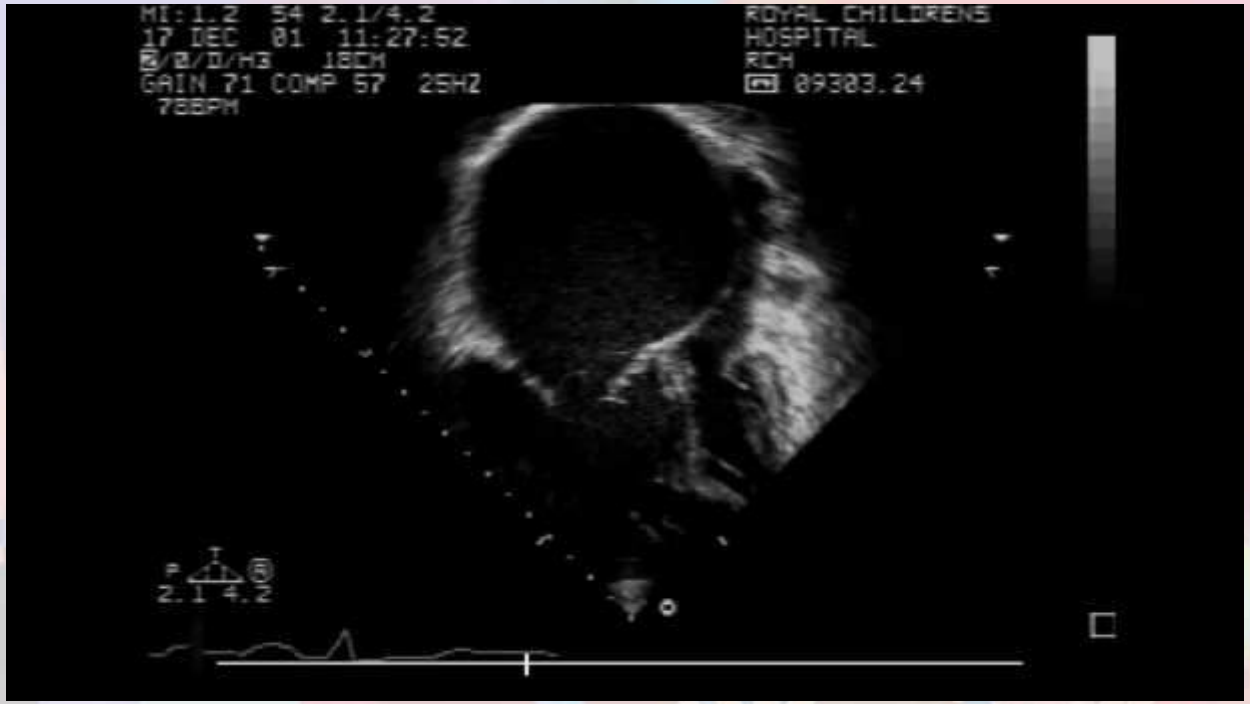
Carl Brookes, MRCP; Hanne Ravn, PhD; Paul White, BSc; Ulla Moeldrup, MD;
Paul Oldershaw, FRCP; Andrew Redington, FRCP

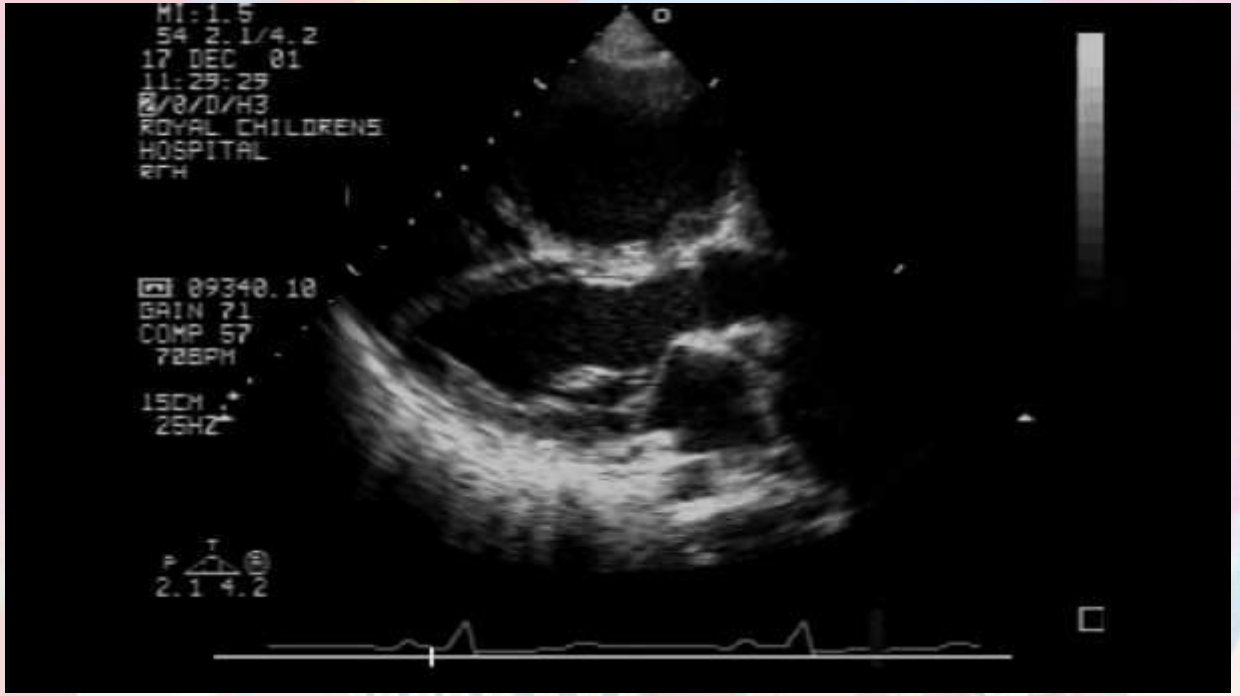


R-L Interactions – Shared Fibers



R-L Ventricular Interactions – Pulmonary Hypertension

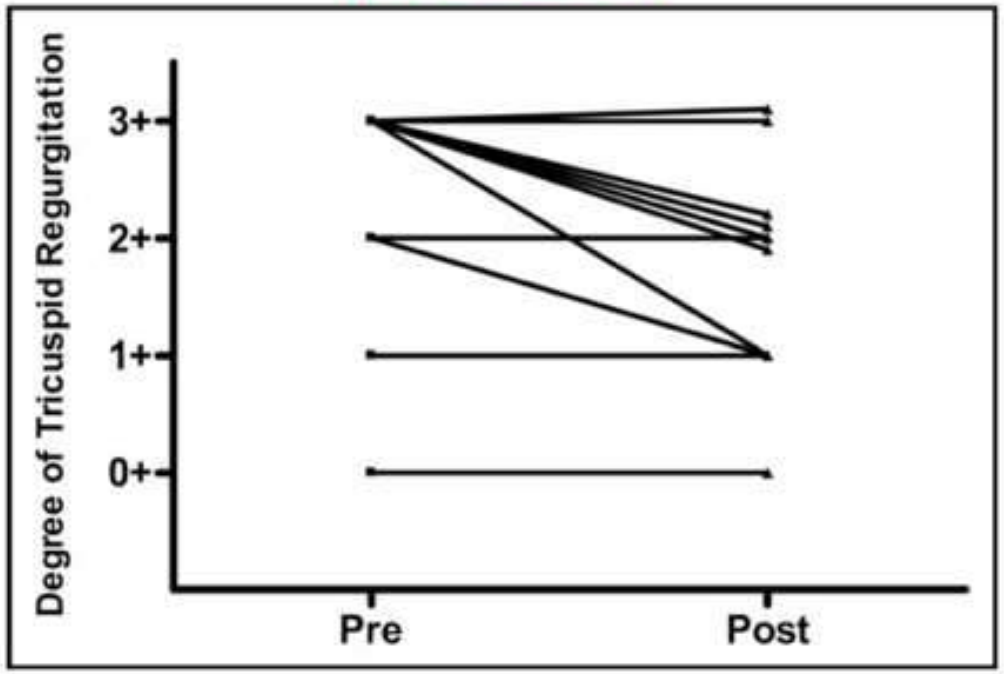




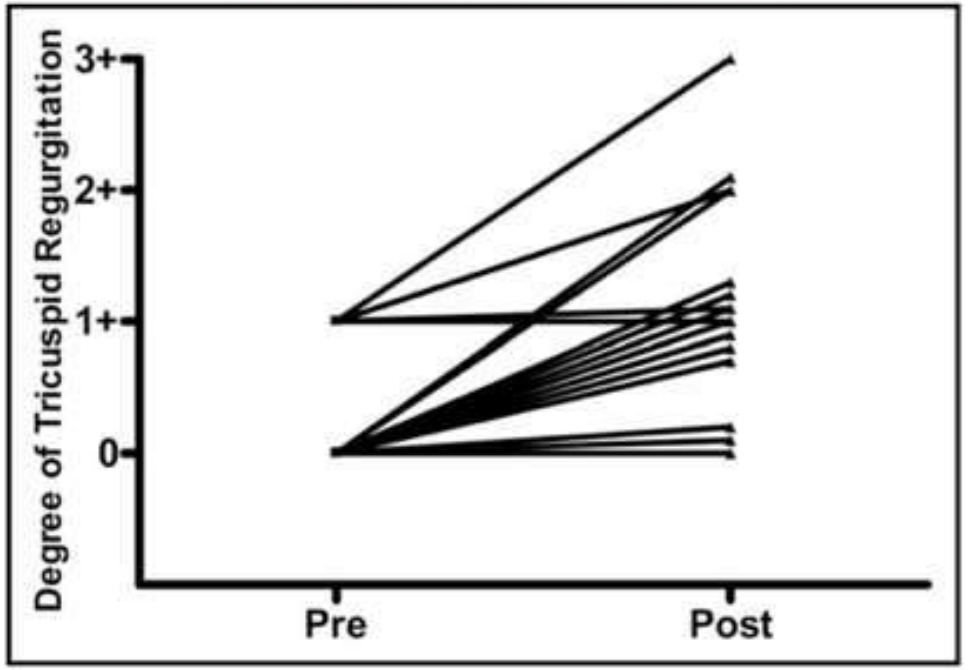
Effects of Morphologic Left Ventricular Pressure on Right Ventricular Geometry and Tricuspid Valve Regurgitation in Patients With Congenitally Corrected Transposition of the Great Arteries

Catharine A. Kral Kollars, MD[a], Sarah Gelehrter, MD[a], Edward L. Bove, MD[b], and Gregory Ensing, MD[a,*]

Procedure That Increases LV Pressure (PA Banding)



Procedure That Reduces LV Pressure (Physiological Repair)



LV Rotational Mechanics in Tetralogy

Journal of Cardiovascular Magnetic Resonance

RESEARCH Open Access

Impact of pulmonary valve replacement on left ventricular rotational mechanics in repaired tetralogy of Fallot

Jamie K. Harrington[1,2*], Sunil Ghelani[1,3], Nikhil Thatte[1,2], Anne Marie Valente[1,3,7], Tal Geva[1,2], Julia A. Graf[1], Minmin Lu[1], Lynn A. Sleeper[1,3] and Andrew J. Powell[1,3]

Abstract

Background: In repaired tetralogy of Fallot (rTOF), abnormal left ventricular (LV) rotational mechanics are associated with adverse clinical outcomes. We performed a comprehensive analysis of LV rotational mechanics in rTOF patients using cardiac magnetic resonance (CMR) prior to and following surgical pulmonary valve replacement (PVR).

Methods: In this single center retrospective study, we identified rTOF patients who (1) had both a CMR ≤ 1 year before PVR and ≤ 5 years after PVR, (2) had no other intervening procedure between CMRs, (3) had a body surface area > 1.0 m² at CMR, and (4) had images suitable for feature tracking analysis. These subjects were matched to healthy age- and sex-matched control subjects. CMR feature tracking analysis was performed on a ventricular short-axis stack of balanced steady-state free precession images. Measurements included LV basal and apical rotation, twist, torsion, peak systolic rates of rotation and torsion, and timing of events. Associations with LV torsion were assessed.

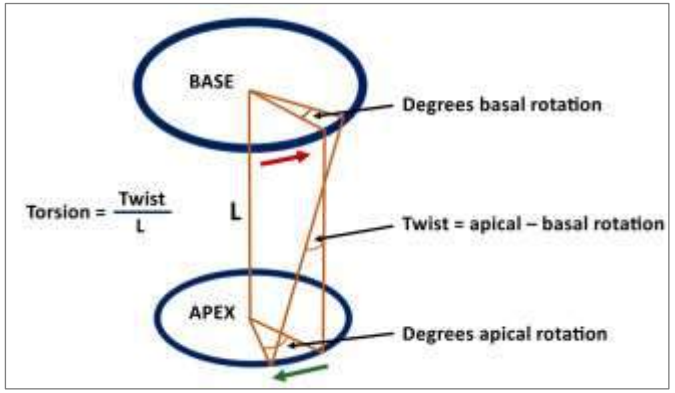
Results: A total of 60 rTOF patients (23.6 ± 7.9 years, 52% male) and 30 healthy control subjects (20.8 ± 3.1 years, 50% male) were included. Compared with healthy controls, rTOF patients had lower apical and basal rotation, twist, torsion, and systolic rotation rates, and these parameters peaked earlier in systole. The only parameters that were correlated with LV torsion were right ventricular (RV) end-systolic volume (r = −0.28, p = 0.029) and RV ejection fraction (r = 0.26, p = 0.044). At a median of 1.0 year (IQR 0.5–1.7) following PVR, there was no significant change in LV rotational parameters versus pre-PVR despite reductions in RV volumes, RV mass, pulmonary regurgitation, and RV outflow tract obstruction.

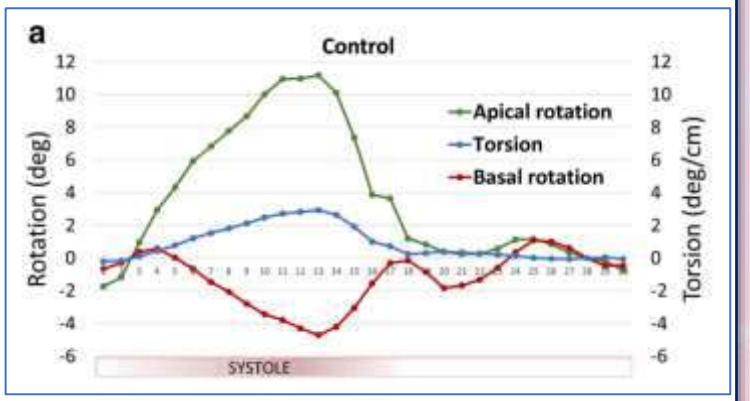
Conclusion: In this comprehensive study of CMR-derived LV rotational mechanics in rTOF patients, rotation, twist, and torsion were diminished compared to controls and did not improve at a median of 1 year after PVR despite favorable RV remodeling.

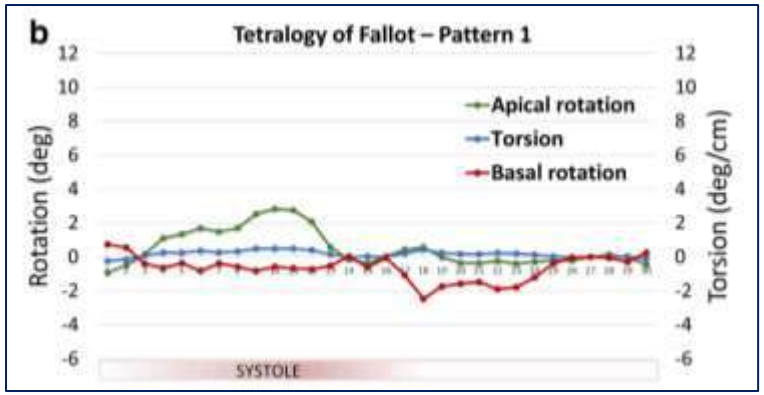
Keywords: Feature tracking, Magnetic resonance imaging, Tetralogy of Fallot, Rotational mechanics, Twist, Torsion, Pulmonary valve replacement

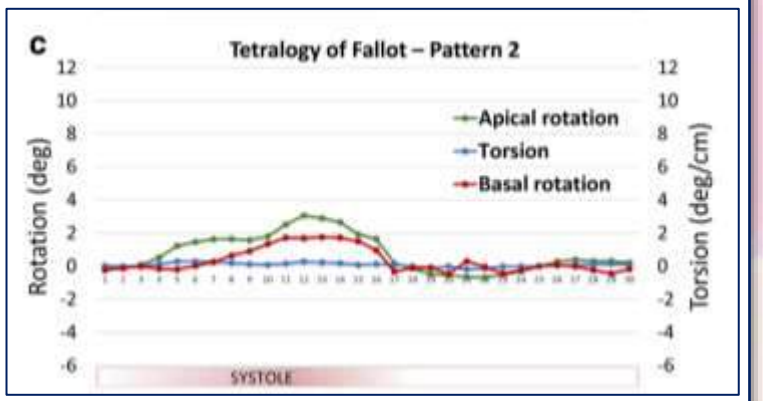
Background

Patients undergoing surgical repair of tetralogy of Fallot (rTOF) have excellent short-term survival [1–3]; however, they have an increased risk of heart failure, arrhythmia, and mortality later in life [4–7]. These sequelae are believed to be in part related to chronic pulmonary regurgitation (PR) and/or stenosis, and their adverse impact



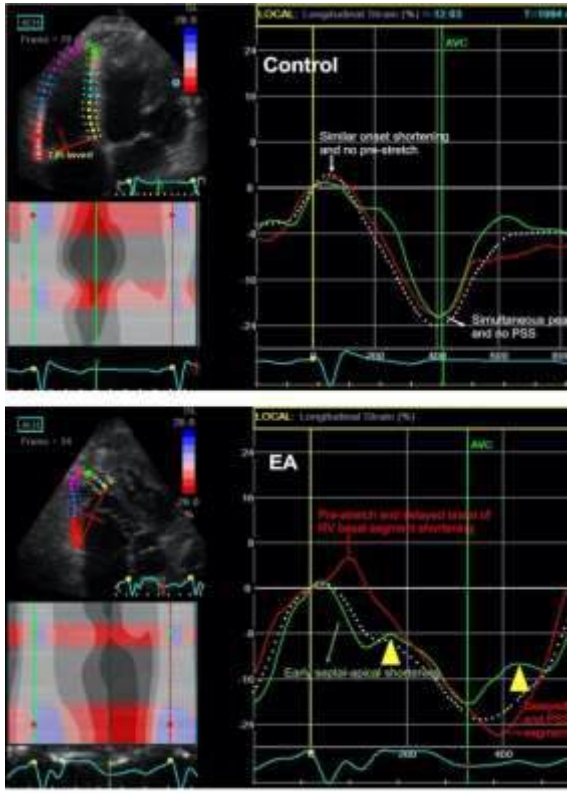






Right Ventricular Electromechanical Dyssynchrony and Its Relation to Right Ventricular Remodeling, Dysfunction, and Exercise Capacity in Ebstein Anomaly

Yohei Akazawa, MD, PhD, Tao Fujioka, MD, PhD, Kana Yazaki, MD, PhD, Martina Strbad, MSc, Jürgen Hörer, MD, PhD, Andreas Kühn, MD, Wei Hui, MD, Cameron Slorach, RDCS, Christoph Roehlig, MD, Luc Mertens, MD, PhD, Bart H. Bijnens, PhD, Manfred Vogt, MD, PhD, and Mark K. Friedberg, MD, *Toronto, Ontario, Canada; Munich, Germany; and Barcelona, Spain*



JACC: CARDIOVASCULAR IMAGING
VOL. 12, NO. 5, 2019
ISSN 1936-878X/$36.00

iMAGE

LETTERS TO THE EDITOR

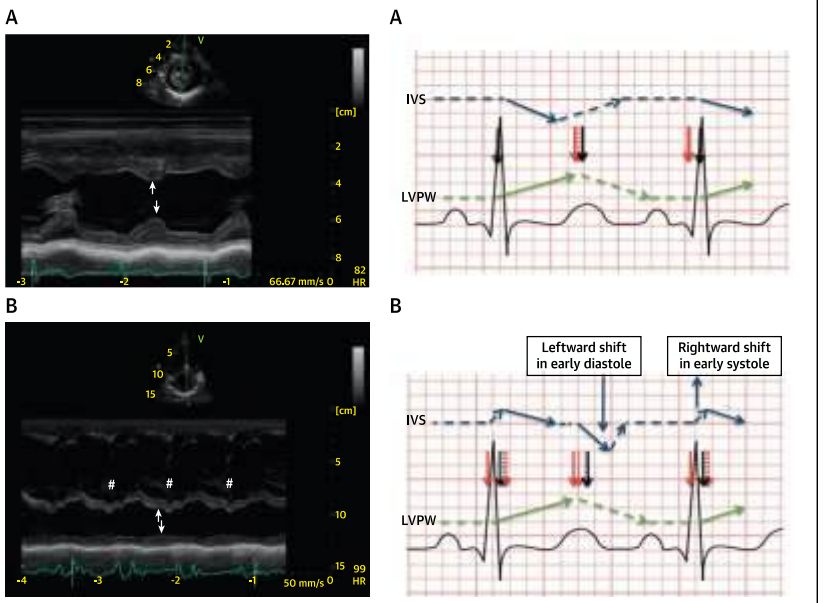
Impact of Interventricular Interactions on Left Ventricular Function, Stroke Volume, and Exercise Capacity in Children and Adults With Ebstein's Anomaly

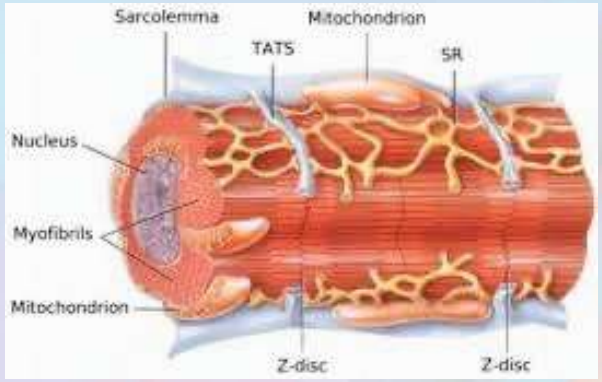
Right ventricular (RV) and left ventricular (LV) interventricular interactions in relation to exercise intolerance are incompletely characterized in Ebstein's anomaly (EA) (1). Pre-operative children and adults with EA and control subjects of similar age distribution were prospectively recruited in Munich, Germany, and children with EA and control subjects of similar age distribution were retrospectively

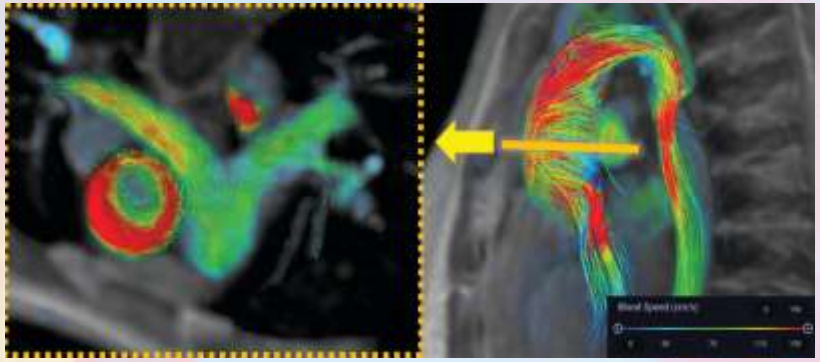
Patients with EA had moderate or severe TR. Compared with control subjects, fractional area change (40.3 ± 13.5 vs. 45.4 ± 5.2, p < 0.001) and the tricuspid annulus systolic tissue Doppler velocity (s') (10.4 ± 1.6 vs. 11.9 ± 3.8, p < 0.001) were lower in EA, and tricuspid annular plane systolic excursion was higher (29.4 ± 9.1 vs. 23.9 ± 4.1, p < 0.001). LVEF (53.4 ± 13.9 vs. 66.1 ± 5.5, p < 0.001), LVLS (n = 57; 18.1 ± 3.3% vs. 20.1 ± 2.3%, p < 0.001), E (peak early diastolic mitral inflow velocity) (68.1 ± 18.1 cm/s vs. 92.1 ± 36.1cm/s, p < 0.001), E/A ratio (the ratio of early diastolic to late diastolic [A] peak mitral inflow velocities) (1.38 ± 0.53 vs. 1.89 ± 0.64, p < 0.001), and the lateral mitral annulus early diastolic tissue Doppler velocity (e') (10.4 ± 4.2 vs. 12.5 ± 3.2, p < 0.001) were reduced in EA.

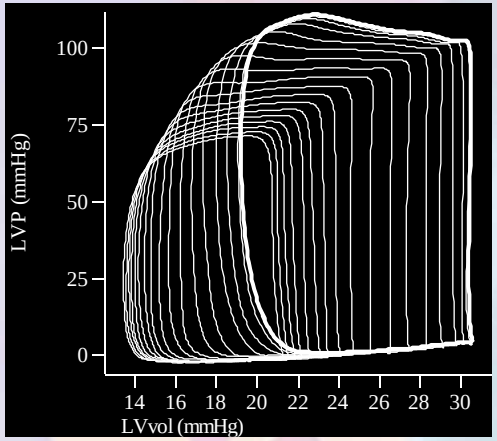
A total of 67 patients had cardiac magnetic resonance on same day as echocardiography. Patients

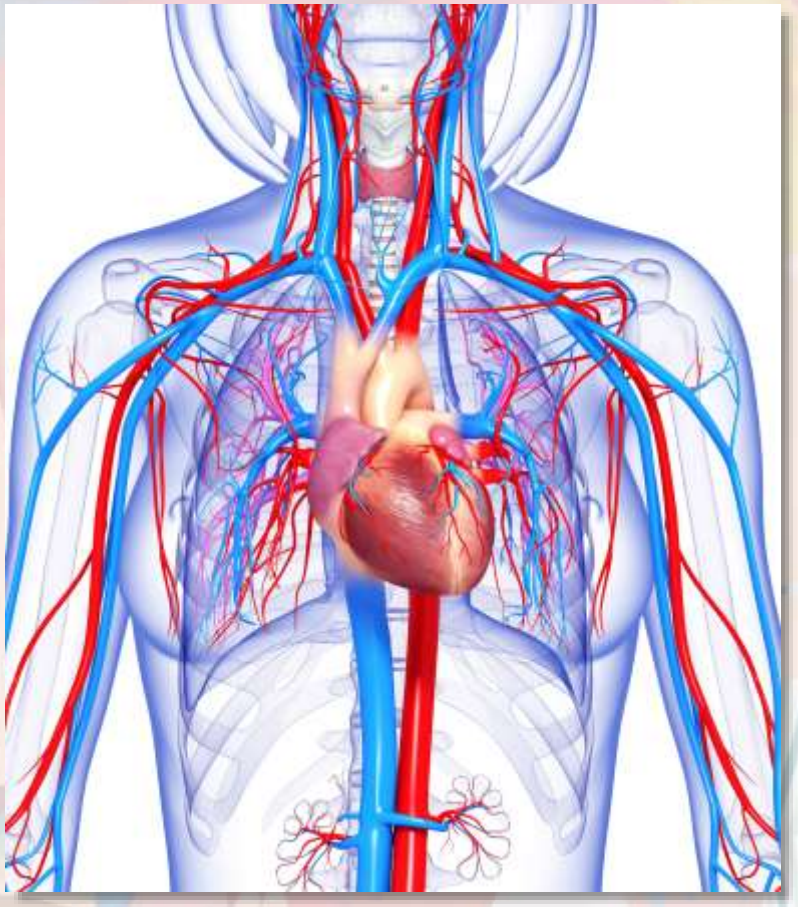
FIGURE 1 Cardiac Cycle Events and Interactions

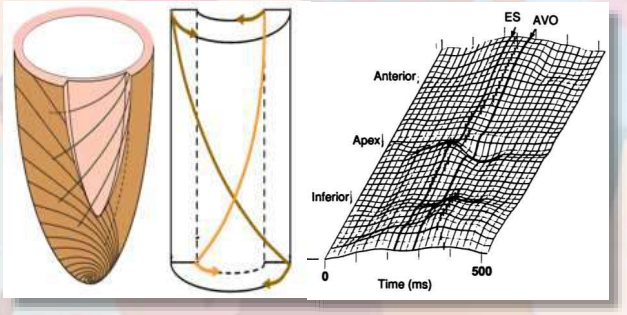


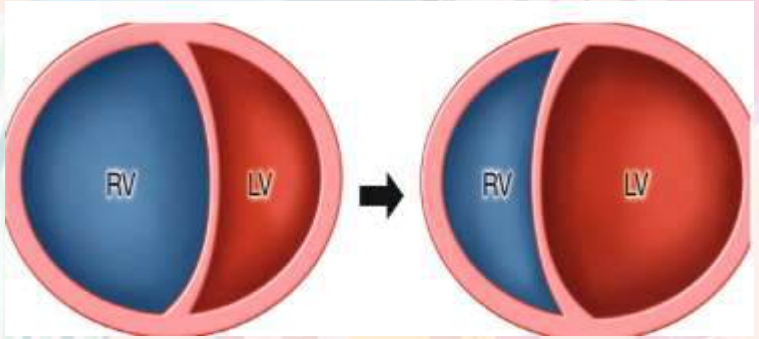












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