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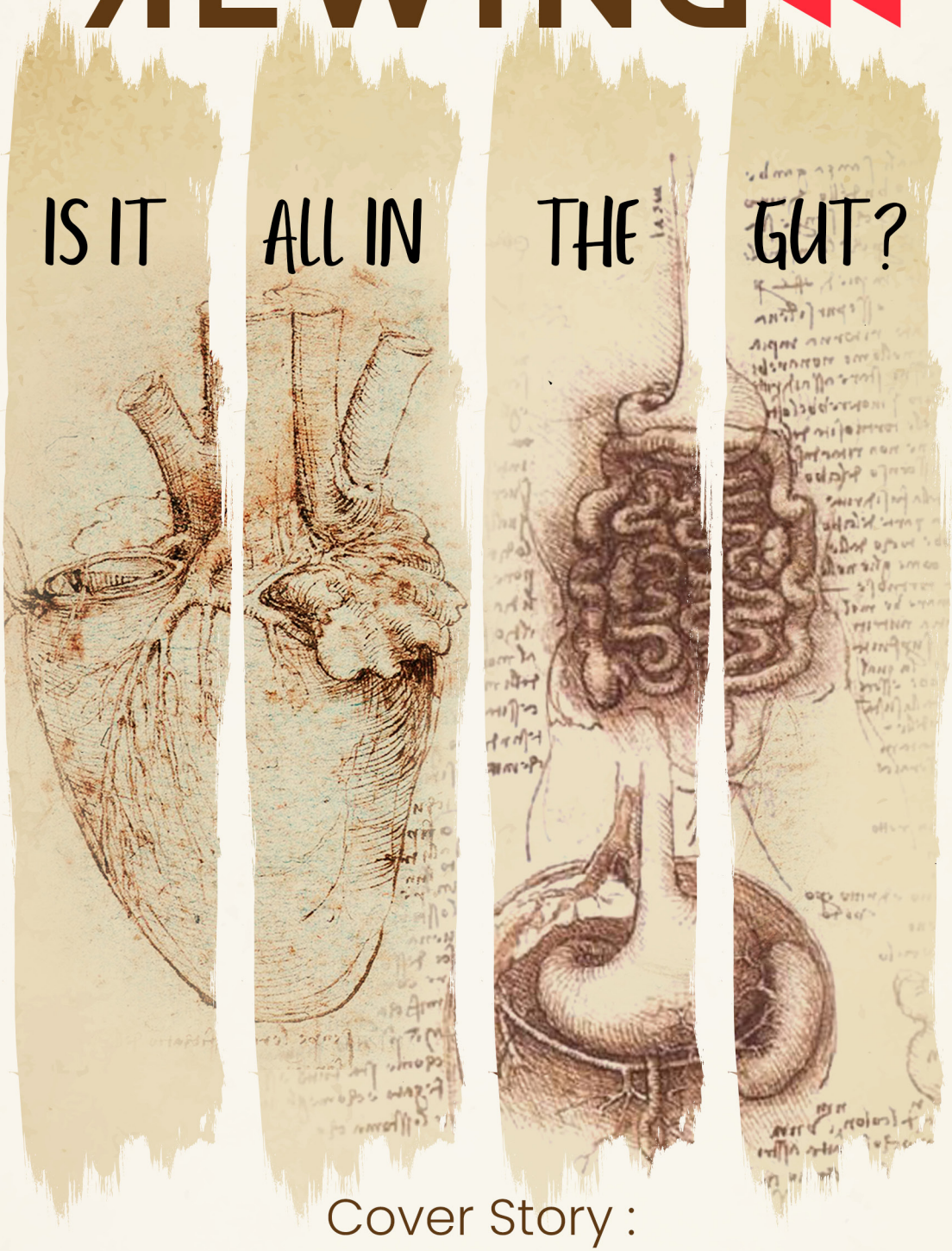
HEART FAILURE REWIND



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Gut Microbiome and Heart Failure

HEART FAILURE ASSOCIATION OF INDIA
Improving Heart Failure Care

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MESSAGE FROM
PRESIDENT, HFAI

Hi everyone,

Greetings from Heart Failure Association of India. In this era of information explosion, it is difficult for someone to keep abreast of the updates in their area of interest. For example, in heart failure, there are many dedicated journals publishing articles on heart failure regularly. In a busy practice like in cardiology, it is a challenge for someone to remain updated. In this context, HFAI has decided to come up with a new newsletter- "HF Rewind", where the academic content is presented in a very simple and easily readable format. Heart failure topics related to cardiology and cardiac surgery will be included.

We are trying to have the updates about latest trials and studies. In addition, we will bring to you core concepts in HF in a palatable format. We also have segments like Clinics, Perspectives, Crossword, Case reports etc. We are supported by a very good team of young generation cardiologists who are behind this attempt. We welcome your suggestions and also contributions.

Wishing you a safe 2021.

Dr. Harikrishnan S
President, HFAI

Yes, We Can

Can we beat Chemotherapy induced HF ?

Dr. Susan Dent
MD, Professor of Medicine Associate Director of Breast Cancer Clinical Research Co-Director, Duke Cardio-Oncology Program

Email: susan.dent@duke.edu

Cancer Therapy Related Heart Failure - Can we do better?

Modern cancer therapeutics has led to significant gains in clinical outcomes for cancer patients, however these gains may be offset by the potential risk of cancer therapy related cardiac dysfunction (CTRCD). While there are several potential cardiovascular consequences of cancer therapy (e.g QTc prolongation, arrythmias, hypertension), heart failure remains a potential devastating consequence of cancer treatment.

Cytotoxic Cancer Therapy and HF

Anthracyclines (e.g. doxorubicin, epirubicin) continue to play a major role in the treatment of both solid (e.g. sarcoma, breast) and hematological (e.g. lymphoma) malignancies, but are associated with a dose-dependent progressive cardiac dysfunction that clinically manifests as heart failure . Historically, doxorubicin-induced heart failure has been reported to increase with cumulative doses (3-5 % at 400 mg/m2; 7-26 % at 550 mg/m2) . However, our increased understanding of the mechanisms of cardiotoxicity in combination with the recognition of the short and long –term consequences of anthracycline exposure on cardiovascular health has led experts to ask - is there really a safe dose of anthracyclines? The American Society of Clinical Oncology (ASCO) guideline on 'Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers' highlighted that cancer patients exposed to lower-dose anthracyclines (e.g. doxorubicin < 250 mg/m2) are also at increased risk of cardiotoxicity, including heart failure, particularly in the presence of additional risk factors including older age (>60 years), compromised cardiac function (borderline LVEF 50-55%), history of myocardial infarction or valvular heart disease or >2 cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia and obesity) during or after completion of therapy (5). Cancer treatment-induced HF occurs with several other traditional chemotherapeutic agents including cyclophosphamide (1-5 %) and docetaxel (1-5 %).

Targeted Agents and HF

Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2), revolutionized the treatment of breast cancer demonstrating significant improvements in both disease-free and overall survival in early stage disease, and progression free survival in advanced disease. However, trastuzumab is associated with an increased risk of cardiotoxicity, including asymptomatic declines in left ventricular ejection fraction (LVEF) and HF. Adjuvant breast cancer trials, where trastuzumab was administered following anthracycline containing regimens, reported an incidence of cardiotoxicity (HF) of 3-4 % ,which did not appear to increase over time, although these trials were in highly selected patients. In clinical practice, higher rates of asymptomatic drops in LVEF and heart failure have been reported .

Other anti-HER-2 targeted therapies such as pertuzumab, (a monoclonal antibody against HER2) given in combination with trastuzumab and chemotherapy , and TDM-1,(trastuzumab linked to DM1), have resulted in further improvements in clinical outcomes in the treatment of breast cancer – but is there an increased risk of left ventricular dysfunction ? While several studies with dual Her-2 targeted therapy have failed to demonstrate an increased risk of heart failure, it should be noted that these trials excluded patients with underlying heart disease and/ or significant co-morbidities and may not reflect the population of patients treated in the real world setting . This is particularly important for patients exposed to sequential anti-HER2 therapies in the advanced breast cancer setting, where there is no long term cardiac safety data. Interestingly, no additional CV toxicity signals have been observed with less commonly used targeted drugs in the treatment of breast cancer such as neratinib (oral irreversible pan -ErbB receptor tyrosine kinase inhibitor) . While it is important to consider a cancer patient's risk of developing LV dysfunction or heart failure with HER-2 targeted agents, this must always be evaluated in the context of the potential benefit of the cancer treatment. After more than a decade of experience, clinicians have become more accustomed to LV changes with HER-2 agents, and are now more likely to advocate for HER-2 targeted therapy in the setting of mild to moderate LV dysfunction, with appropriate medical management, and close cardiac surveillance.

Cardiac dysfunction has also been reported with vascular endothelial growth factor (VEGF) signaling pathway inhibitors (e.g. bevacizumab, sorafenib, sunitinib), as well as some proteasome inhibitors (e.g carfilzomib).

Approach to Cancer Patients at Risk of Cancer Therapy Related Heart Failure.

In 2020 the European Society of Medical Oncology (ESMO) published a consensus statement on "Management of cardiac disease in cancer patients throughout oncological treatment". Several recommendations are provided for patients at risk of cancer therapy related dysfunction, including heart failure. Patients treated with therapies associated with a significant risk of HF or LV dysfunction should have quantitative evaluation of LV ejection fraction and diastolic function prior to initiation of cancer therapy. In select high risk patients (e.g. those treated with high dose anthracyclines > 250 mg/m2), baseline cardiac biomarker evaluation (BNP, Troponin-TNI or TNT) before the initiation of cancer therapy should be considered, as this may identify individuals at greatest risk for developing LV dysfunction. Cardioprotective therapy with ACE inhibitors or ARBs and/or beta-blockers should be considered for cancer patients with cardiovascular risk factors exposed to potentially cardiotoxic therapy, those with borderline LV function (40-50%) at baseline, and no alternative non-cardiotoxic cancer therapy. The incorporation of global longitudinal strain (GLS) assessment into the echocardiogram protocol may be useful in the earlier identification of patients at risk of developing heart failure, and lead to earlier introduction of medical therapy and avoidance of permanent LV dysfunction.

As oncologists, our goal is to provide optimal therapy for all cancer patients diagnosed with early or advanced disease. Avoiding the cardiovascular consequences of anti-cancer treatment, including heart failure, requires a multidisciplinary approach with close collaboration among oncologists, cardiologists, nurses, pharmacists and allied health care professionals. In 2021 we have the knowledge to decrease the risk of cancer therapy related LV dysfunction and heart failure – As health care providers, it is our responsibility to ensure that patients have access to this knowledge and approach.

Suggested Reading

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Practice changing trials of 2020

2021 – What's New in Heart Failure Management?

Dr. Abhilash S P

MD, DM
Additional Professor in Cardiology
Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvanathapuram, Kerala

Email: abhispin@gmail.com

2021 - What's new in heart failure management?

2020 would be remembered as the year of covid-19 and the entire world was forced to witness and accept a new normal in life. Despite the overwhelming importance given to the research to curb pandemic, there were a few advances in heart failure management which could change our practice in 2021.

The EMPEROR-Reduced trial - Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure[1]

- Sodium–glucose cotransporter 2 (SGLT2) inhibitors could reduce the risk of hospitalization for heart failure.
- Patients with class II, III, or IV heart failure and an ejection fraction of 40% or less received empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy.
- Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes.
- Empagliflozin-treated patients had better renal outcomes on follow up.
- Uncomplicated genital tract infection was reported more frequently with empagliflozin.
- Compared to DAPA-HF trial2, the patients in this trial had on average more severe heart failure, with a mean ejection fraction of 27% versus 31%.

The EAST-AFNET 4 trial - Early Rhythm-Control Therapy in Patients with Atrial Fibrillation[3]

- Patients who had early atrial fibrillation (diagnosed ≤1 year before enrolment) received either early rhythm control or usual care.
- Early rhythm control included treatment with antiarrhythmic drugs or atrial fibrillation ablation after randomization.
- Usual care limited rhythm control to the management of atrial fibrillation–related symptoms.

- The primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome.
- Early rhythm-control therapy was associated with a lower risk of adverse cardiovascular outcomes than usual care among patients with early atrial fibrillation.
- Serious adverse events related to rhythm-control therapy occurred in 4.9% of the patients assigned to early rhythm control and 1.4% of the patients assigned to usual care.

The RATE AF trial - Effect of Digoxin vs Bisoprolol for Heart Rate Control in Atrial Fibrillation on Patient-Reported Quality of Life[4]

- 160 adults aged 60 years or older with atrial fibrillation and symptoms of heart failure randomized to digoxin (mean attained dose, 161 µg/d) vs bisoprolol (mean attained dose, 3.2 mg/d).
- At 6 months, the mean 36-Item Short Form Health Survey physical component summary scores were 31.5 for the digoxin group vs 29.3 for the bisoprolol group.
- Among patients with permanent atrial fibrillation and symptoms of heart failure treated with low-dose digoxin or bisoprolol, there was no statistically significant difference in quality of life on follow up.

The VICTORIA trial – Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction[5]

- Vericiguat is a novel oral soluble guanylate cyclase stimulator.
- Phase 3, randomized, double-blind, placebo-controlled trial, 5050 patients with chronic heart failure (class II, III, or IV) and an ejection fraction of less than 45% received vericiguat (target dose, 10 mg once daily) or placebo, in addition to guideline-based medical therapy.
- The primary outcome was a composite of death from cardiovascular causes or first hospitalization for heart failure.
- Among patients with high-risk heart failure, the incidence of death from cardiovascular causes or hospitalization for heart failure was lower among those who received vericiguat than among those who received placebo.

The MAVERICK-HCM trial

[Evaluation of Mavacamten in Symptomatic Patients with Non-obstructive Hypertrophic Cardiomyopathy[6]]

- Mavacamten is a first-in-class reversible inhibitor of cardiac-specific myosin.
- Multi-centre, double-blind, placebo-controlled, dose-ranging phase II study in adults with symptomatic non obstructive HCM (functional class II/III), left ventricular ejection fraction (LVEF) ≥55%, and N-terminal pro−B-type natriuretic peptide (NT-proBNP) ≥300 pg/ml.
- Mavacamten was well tolerated in most subjects and treatment was associated with a significant reduction in NT-proBNP and cTroponin I, suggesting improvement in myocardial wall stress.

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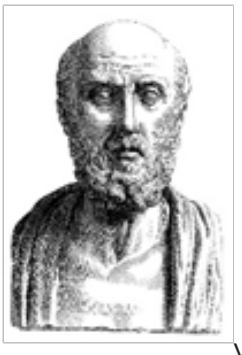
Is It all in the Gut?
Cover Story:
Gut Microbiome and Heart Failure

Dr. Harikrishnan S
MD, DM
Professor of Cardiology
SCTIMST, Trivandrum, Kerala
Email: drharikrishnan@outlook.com



"All diseases begin in the gut." Hippocrates (460 – 370 BC.)

You might be wondering, why you, after so much dieting, are not able to reduce even a single kilo, but your close friend, who eats a lot, remains lean to your envy

The answer to this puzzle could be the living community inside you - the microorganisms colonized in your gut - called the "gut microbiome". Mostly they are bacteria, but it can be fungi and other living forms also. It is found that those people having higher 'Firmicutes' bacterial population in their gut gain more weight than those people with the abundance of Bacteroides species, having the same diet. Such "obese microbiome" has an increased capacity to harvest energy from the diet. Is it only a theory or can you prove this?

Yes, it is found that this "Obese trait" is transmissible: fecal transplantation of germ-free mice with an 'obese microbiome' results in a significantly greater increase in total body fat than colonization with a 'lean microbiota', with the same diet.

In the last few years, many research articles have brought out the relation between the gut microbiota and many diseases including heart failure.

What is Human Gut Microbiome?

The healthy human harbors ~100 trillion bacteria in the gut, which includes 1000 –1500 bacterial species. The microbiome is constantly making compounds, some of which may get absorbed and are biologically active.

The gut microbiome is acquired from the environment; it is not genetically acquired. Human gut microbiome Is dominated by 4 large groups of bacteriaor phyla: Bacteroides, Firmicutes, Actinobacteria and Proteobacteria.

What decides the pattern of your Gut Microbiome?

One of the most important factos which result in the gut microbial pattern is your long term diet. For example diet high in animal protein and fat have high levels of Bacteroides and low levels of Prevotella. On the contrary, diet high in carbohydrates but low in animal protein and fat will have low levels of Bacteroides and high levels of Prevotella.

Association of Gut microbia and Heart failure

There are many recent publications and research regarding the association of gut microbia and diabetes mellitus,hypertension, coronary artery disease and heart failure.

In heart failure, there is ventricular dysfunction and thus reduction in intestinal blood flow and low oxygen delivery. This predispose to the growth of pathogenic types of anaerobic bacteria in the intestine. These bacteria produces many harmful substances including TMAO and endotoxin (lipopolysaccharides- LPS) which predisposes or leads to worsening of heart failure. The precursor of TMAO is L-Carnitine or Choline which is present in food substances like red meat. If you have high intake of red meat, TMAO production is increased and can get absorbed into the system. These discoveries have lead to the concept of "Heart-Gut axis" or "Heart – Gut hypothesis" of Heart Failure.

Can we manipulate the gut microbiome and treat diseases?

We can alter the diet and change the type of microbia. We can target the chemicals produced by the gut microbia or we can directly alter the microbial flora by giving probiotics.

If we reduce red meat in diet, we reduce intake of choline and lecithin and there by reduce TMAO with all positive effects in heart failure. Adopting a Mediterranean diet has shown to reduce markers of heart failure. Administering non-absorbable antibiotics to kill specific microbiota and thus alter the microbial pattern is one method, but has many clinical implications.

Future.

The co-habitation between us and our gut microbia who actually control our systems remotely has been there for millions of years . Understanding and probably manipulating them favourably may hold the future for health and disease.

Probiotic use is another method of changing the gut microbial pattern. Probiotics are live beneficial bacteria (Bifidobacteria, Lactobacilli, Streptococci and non-pathogenic strains of E. coli) that can be ingested to alter and create an appropriate intestinal microbial balance. There are studies using Saccharomyces boulardii in heart failure which showed benefit.

The last but, very interesting method which is gaining popularity in many gastrointestinal diseases is Fecal transplantation. Fecal transplantation from lean volunteers were found to benefit by weight reduction and also reduction in risk factor levels of heart failure.

Epilogue:

"No disease that can be treated by diet should be treated with any other means."

Moses Maimonides :
Medieval Jewish philosopher and one of the greatest Torah scholars and physicians of the Middle Ages

Clinics

Utility of Bendopnea in Heart Failure

Dr. Sajan Ahmad Z
MD, DM, DNB
Associate Professor of Cardiology
Pushpagiri Medical College
Thiruvalla, Kerala
Email: sajanahmad@gmail.com

Q1. What exactly is bendopnea ?

A1. Bendopnea is shortness of breath or dyspnea on bending forward. It is a relatively newly described symptom of heart failure (HF). In 2014, Thibodeau et al described it in 28% of patients with systolic HF who were referred for right heart catheterization.

Q2. Is 'kamptopnea' a better term to describe this phenomenon?

A2. What is in a name? As Kamptos in Greek means 'bent over', kamptopnea would be a more traditional term like 'orthopnea' and 'platypnea'. On the other hand, it might really sound Greek to patients, for whom bendopnea would be a more understandable term !

Q3. How can this symptom be 'elicited' ?

A3. Ask the patient to sit in a chair. Instruct him/her to bend forward at the waist as if to put on shoes/socks and touch the feet with their hands. Bendopnea is generally defined as dyspnea occuring within 30 seconds of bending forward, even though most patients developed this within 10 seconds (median time to onset of 8 seconds).

Q4. What is the mechanism of bendopnea ?

A4. Bending causes increased intrathoracic pressure. This leads to a further increase in ventricular filling pressures (LV>RV) in HF patients who have already elevated filling pressures. Another reason could be that bending causes an increase in intraabdominal pressure (similar to what happens during a hepatojugular reflux maneuvre), along with compression and/or upward mechanical displacement of a congested liver.

Q5. Are there any hemodynamic correlates of bendopnea ?

A5. Patients with bendopnea have higher supine pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP). A hemodynamic pattern of high PCWP with low cardiac index (CI) was seen more commonly among these patients. The median increase in PCWP with bending was 8-9 mm Hg. On cardiopulmonary exercise testing (CPET), patients with bendopnea have a higher minute ventilation to carbon dioxide production slope (VE/VCO2 slope).

Q6. How reliable is it as an indicator of HF ?

A6. Bendopnea has been described in 18-49% of patients with HF. However, it has been documented in pulmonary disorders and morbid
obesity too.

Q7. Is there a prognostic role for bendopnea ?

A7. Seems so. Presence of bendopnea has been correlated with adverse outcomes in ambulatory patients with HF. It is also linked to more advanced New York Heart Association (NYHA) functional class and higher mortality among hospitalised patients with HF. In patients undergoing surgical aortic valve replacement (SAVR) for severe aortic stenosis, bendopnea has beenfound to be associated with smaller aortic valve area, higher pulmonary artery systolic pressure and prolonged mechanical ventilation and length of hospitalisation after SAVR. Among patients with pulmonary hypertension, those with bendopnea were found to have shorter 6 minute walk distance, higher NTpro BNP level and lower TAPSE (tricuspid annular plane systolic excursion).

Suggested Reading

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Exercise and Heart Failure

Dr. James Thomas
MD, DM
Consultant Cardiologist
Bharath Hospital Kottayam
Kerala, India
Email: drjamescardio@gmail.com

1. Before discussing the benefit of exercise in established heart failure (HF), let us start from the beginning...Will regular exercise prevent HF? And do we have data?

Regular exercise is indeed protective against HF. NHANES 1, FINMONICA, and even the Framingham data says the same thing[1,2,3]. The relationship between the probability of having HF and long-term cardiorespiratory fitness and exercise has been clearly established. The association is strong, inverse and independent of other variables...period.

2. The postulate that exercise prevents HF sounds pretty vague. Is there really a dose – effect relationship between exercise and the chance of developing HF?

A 1 unit higher cardiorespiratory fitness has been found to be associated with 6% lower risk of incident HF events corresponding to a 21% lower risk of HF per 1 metabolic equivalent (MET) greater of cardiorespiratory fitness[4]. If you put in 500 METs-min/week of physical activity, you have a 10% lower risk of HF compared with those with no physical activity. But if you pump in 1000 or 2000 METs-min/week, that has been shown to result in a 19% and 35% lower risk of HF, respectively. A linear dose response across a wide dose range without upper or lower threshold effect has been observed in most studies, suggesting that *'more activity is better than some activity'* for HF prevention.

3. So it is clear that low cardio respiratory fitness puts you at a higher risk for HF. But is the risk more for HFpEF or HFrEF?

Studies have shown that association of low cardiorespiratory fitness and HF is more likely to be with HFpEF rather than in HFrEF. In fact, the data for dose-dependent protective effect of physical activity on HF risk is also more robust for HFpEF than for HFrEF. [4,5]

4. What about the benefits of exercise in established HF? And moreover, is exercise therapy safe in HF? Is the data strong..?

Several systematic reviews and meta-analyses of small studies have shown that physical conditioning by exercise training in HF is safe and improves exercise tolerance, health-related quality of life and HF hospitalization rates. A single large RCT, the **HF ACTION** trial, showed a modest and non-significant reduction in the primary composite outcome of all-cause mortality or all-cause hospitalization. More importantly no safety concerns were raised, proving that exercise therapy is safe in HF [7]. In a Cochrane review of exercise training which included 33 trials with 4740 HF patients, there was a trend towards a reduction in mortality and HF related hospitalization and improved quality of life, again without any safety issues[8].

5. Do we have evidence for the benefits of exercise in HFpEF too?

There is evidence that in patients with HFpEF too, exercise training has several benefits, including improvements in exercise capacity, as measured objectively using peak oxygen consumption, quality of life and echo assessment of diastolic function.

6. Which HF patient should I choose and not choose for exercise training and rehabilitation?

Exercise training is usually recommended for stable NYHA class I–III HF patients . But even for those who have been hospitalized with a decompensated HF episode, early mobilization through an individualized exercise programme can be tried cautiously after discharge. There are of course a few contra indications for exercise training and testing which are listed in Table 1.[9]

7. How to safely start an exercise programme for a Heart failure patient?

Gradual mobilization/calisthenics, respiratory training, and small muscle strength exercise etc should be started initially, rather than straightaway jumping into exercise therapy. Exercise capacity should be ideally assessed before starting exercise training by cardiopulmonary stress testing using treadmill or bicycle ergometer. If this is not possible, at least a 6 min walk test should be considered. Once exercise capacity is assessed, proper exercise training can be started.

Table 1 Summary of contraindications to exercise testing and training (A), exercise training (B), and increased risk for exercise training (C)

(A) Contraindications to exercise testing and training
1. Early phase after acute coronary syndrome (up to 2 days)
2. Untreated life-threatening cardiac arrhythmias
3. Acute heart failure (during the initial period of haemodynamic instability)
4. Uncontrolled hypertension
5. Advanced atrioventricular block
6. Acute myocarditis and pericarditis
7. Symptomatic aortic stenosis
8. Severe hypertrophic obstructive cardiomyopathy
10. Intracardiac thrombus
(B) Contraindications to exercise training
1. Progressive worsening of exercise tolerance or dyspnoea at rest over previous 3–5 days
2. Significant ischaemia during low-intensity exercise (< 2 METs)
3. Uncontrolled diabetes
4. New-onset atrial fibrillation/atrial flutter
(C) Increased risk for exercise training
1. > 1.8 kg increase in body mass over the previous 1–3 days
3. Decrease in systolic blood pressure with exercise
4. NYHA functional class IV
5. Complex ventricular arrhythmia at rest or appearing with exertion
6. Supine resting heart rate >100 b.p.m.

8. What are the various exercise training protocols in HF?

Three different training modalities have been proposed with different combinations:

(1) Endurance aerobic (continuous and interval);

(2) Strength/resistance;

(3) Respiratory

1. Endurance aerobic training (continuous and interval)

Continuous endurance training

Continuous aerobic training is typically performed on a bicycle ergometer or a treadmill , typically at moderate intensity, which allows the patient to perform prolonged training sessions (up to 45–60 min duration). It is the best described and established form of training, because of its well demonstrated efficacy and safety. In more deconditioned patients, it is recommended to start low (i.e. at low intensity for 5–10 min twice a week), and gradually step up.

Interval endurance training

Recently, high intensity interval training (HIIT) has been proposed to be more effective than continuous moderate intensity exercise for improving cardiorespiratory function. HIIT is characterized by alternating short periods (10-30 sec) of exercise at ≥80% of one's VO_2 peak with longer periods (60-80 sec) of less intense (40–50% of VO_2peak) recovery.

HIIT has been shown to be safe in HF patients and has even scored better than continuous training in parameters like aerobic capacity in a few studies.[11,12]

Resistance/strength training

Resistance/strength training (RST) is a muscle contraction performed against a specific opposing force thereby generating resistance, such as lifting weights. It strengthens and tones muscles and increases bone mass and has been proposed as an anabolic intervention to help prevent the wasting syndrome.

Even though concerns about a detrimental effect of increased afterload during the RST on left ventricular function caused by have not been confirmed, the current evidence in favour of RST is not as robust as that of endurance aerobic training. RST can probably complement, but not substitute endurance training in HF.

Respiratory training

Trials using inspiratory muscle training in CHF patients suggest that such an intervention can improve exercise capacity and quality of life. It has been suggested to start respiratory training at 30% of the maximal inspiratory mouth pressure and to readjust the intensity every 7–10 days up to a maximum of 60%.

9. How does a typical exercise training programme for a chronic HF patient look like?

The choice of the type and intensity of exercise therapy should take into account various factors like age, functional class, comorbidities if any, patient preference and facilities for exercise.

A typical continuous moderate intensity aerobic programme , which is often the most common one chosen, looks like this...

Initial stage (first 1–2 weeks): Intensity should be kept at a low level, especially in patients with NYHA functional class III (50% of peak VO2), and gradually increasing duration from 15 to, say 30 min, according to perceived symptoms and clinical status

Improvement stage: A gradual increase of intensity (to 60%, and even 70–80% of peak VO2, if tolerated) is the primary aim in this stage. Prolongation of exercise duration is a secondary goal and 45-60 min of exercise can be targeted.

Frequency of sessions : Aim for most days of exercise (at least 3 days/week and preferably 6–7 days/ week).

It is recommended to start training in a setting of direct monitoring and supervision, especially during initial sessions and particularly when HF symptoms are severe, and then plan a gradual transition to a home based regime.

10. Exercise Therapy in special populations:

a. Patients with ICD and/ or CRT

A symptom limited cardiopulmonary exercise stress test is mandatory before exercise therapy is started. This helps not only to determine the exercise capacity, but can also assess the chronotropic response to exercise, the presence of exercise-induced arrhythmias, maximum heart rate (HR) in case of onset of an arrhythmia, the effectiveness of pharmacological HR control, and the risk of reaching an HR in the ICD intervention zone. Patients who have experienced symptomatic arrhythmias or ICD discharges should be directed towards exercise modalities in which a short loss of consciousness due to ICD discharge might be less harmful, for example avoiding strenuous swimming or climbing heights.

b. After Transplantation

Persistently abnormal exercise capacity early after cardiac transplantation can be caused by marked deconditioning before transplantation, surgical denervation, skeletal muscle weakness, and corticosteroids . Exercises can be performed in a supervised setting early and patients transferred to a home program once an adequate level of activity is achieved. A walking program is usually recommended initially, with gradual stepping up of exercise intensity. Rate of perceived exertion (eg: Borg scale) is a useful tool to prescribe intensity because the heart rate will not be reflective of effort. An initial low RPE of 11 to 13 is often suggested and every effort should be made to gradually increase the intensity to at least an RPE of 13 to 15 to approach the ventilatory threshold, which may also be improving with training.

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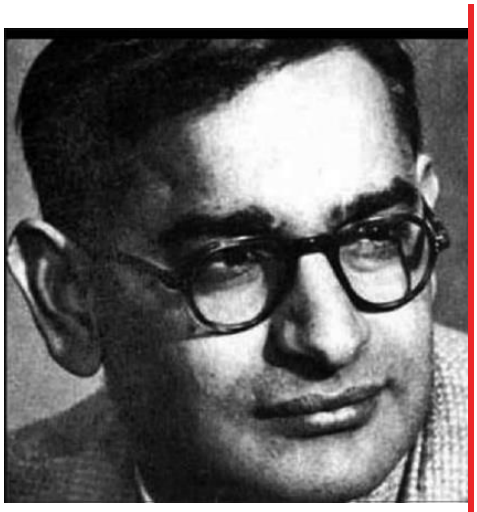

Transplant Number 1

Inspiring Story of the First Human Heart Transplantation in India

Dr. Amit Malviya
MD, DM
Assistant Professor of Cardiology
NEIGRIHMS, Shillong
Email: dramit_malviya@rediffmail.com

&

Dr. Sanjib Rawat
MS, MCh
Assistant Professor,
Department of CTVS, NEIGRIHMS, Shillong
Email: sanjibrawat@gmail.com

"That's all we ever really wanted in the end. It would have been great to be first, but, finally, what always mattered most was that we'd find a way to help people live a little longer so that they could be with those they loved, and do the things they cared about, for a little longer. It was a very simple hope, but we did it. That seems the best memento of all. I'm happy to make an anniversary of that fact." – Norman Shumway: Father of heart transplantation.

Transplantation surgery for a human heart is one of the most fascinating ideas conceived and materialized in the present day medical sciences. Although the first human to human heart transplant in the world was done by Dr . Christiaan Barnard at Groote Schuur Hospital at Cape Town in South Africa, Dr. Norman Shumway is widely considered as the Father of Heart Transplantation due to his pioneering work in this field. India was not far behind in this exciting field of cardiothoracic surgery.

Many of us are not aware that the world's 6th heart transplant (2 months after the first transplant done in South Africa) was done in Mumbai ,India.

It is not a widely known fact that Prafulla Kumar Sen and his team performed India's first human to human heart transplant in Bombay in February 1968, despite it having been a momentous occasion. Dr. Prafulla Kumar Sen performed the surgery at the KEM Hospital in Mumbai on the 16th of February ,1968. As a matter of fact, he had performed the first intracardiac operation of any kind

(closed mitral valvotomy)in the year 1952. A paper on the first human heart transplantation in India was published by Dr P K Sen in the American Journal of Cardiology in December 1968. Dr Sen and his team started many animal experiments between 1962 to 1965 and tested this technique in hundreds of dogs and Dr Sen and his team studied human cadavers for details of the operative anatomy. Finally , they attempted the first case in 1968. The recipient was a male patient with severe progressive cardiomyopathy. The donar was a 20 years old who had sustained severe head injurys after falling from a train. The operation was performed successfully , however the patient died within 3 hours due to acute right heart failure. Dr Sen was the fourth surgeon in the world to attempt transplant way before it began in Europe, Canada, Australia, Japan or the Soviet Union. Again, on 13th September 1968, he performed the second heart transplant in India but this time also, the outcomes were not good and unfortunately, the recipient died within 14 hours.

The initial enthusiasm of heart transplant in 1968 started fading out subsequently . There were a multitude of reasons behind this but the main hurdle was ethical and legal controversies hurting the enthusiasm of doctors. In fact , this situation was not specific for India and early transplant operations world over had not shown promising results in terms of patient survival. In 1971, Life magazine came out with a report titled 'The Tragic Record of Heart Transplants: A New Report on an Era of Medical Failure'. This silent and depressive period lasted for almost three decades till some breakthrough came. In India, legislation of brain death materialized in 1994 and the Organ Transplant Bill 1994 was passed, which legalized organ transplant in India. Meanwhile, in AIIMS, New Delhi, a team led by Dr Panangipalli Venugopal had been working on the transplant program for three years. On August 3rd 1994, they got a donor – a brain dead woman in her mid 30's whose relatives were willing to donate her heart. And thus came the first successful heart transplant in India , a 42 years old male recipient who survived for 14 years after the operation . This marked the beginning of a new era for heart transplantation in India. Dr P Venugopal was awarded Padma Bhushan for this achievement and 3rd August is celebrated as National Heart Transplantation Day.

Perspective

Did The Heart Pass or Fail?

Dr. Tiny Nair
MD, DM
Head, Dept. of Cardiology
PRS Hospital, Trivandrum
Kerala, India
Email: tinynair@gmail.com

The Binary
Pass or fail?

In our school days, there used to be just one answer.

This very important 'do-or-die' question came up every time the school academic year drew to a close. A fail in the class would end up in a rather uncomfortable situation of a one-to-one meeting with the in-house 'law-enforcing officer', the dad, who, those days, had not yet evolved into the friendly financier of today. Despite lack of large RCTs, most dads those days firmly believed that a sharp pull of the ear, coupled with few twists and turns would,in the long term, alter the direction of the sons academic achievement, which eventually, turned out to be inconclusive with a wide confidence interval. A timely appeal from mom, the in-house lawyer, would end the drama. The rituals done we would quickly forget the episode, go back to playing cricket, till the seasonal ailment recurred next December.

'Pass-fail' binary did not predict how our future was going to be. The positive predictive value was simply unknown. The system did not differentiate between a 'dyslectic kid' and a 'genius in the making'. Also, there was no 'mid-range' between pass and fail.
As the understanding and concept of hemodynamic derangement in heart failure (HF) unfolded in clinical medicine, congestion became the hallmark offailure. Edema denoted systemic congestion incriminating the right ventricle (RV) while dyspnea and orthopnoea were considered the fingerprint of a criminal left ventricle (LV). 'Failure' was present if there was congestion, otherwise the heart 'passed'. There was either 'failure' or 'no-failure', a clear binary; nothing in between. The fact that mercurial diuretics did nothing less than making a patient lethargic and confused; mega-dose digoxin ensured nausea and vomiting; the patient mostly succumbed more painfully than the disease itself.

Binary to Continuous Variable

As time passed, things changed. Both assessment of academic 'school' curriculum as well as understanding of severity of heart failure(HF) drastically changed. The aim to predict which 'student' had the sign to excel and who lagged behind, waiting for early help, or which 'heart failure patient' would remain stable and which one did not, came under the spotlight. The binary of 'pass-fail' gave way to an era of 'continuous variable'.

As my son started his schooling, we encountered a different set of problems, His reluctance to go to school, which perhaps was a genetic trait, was just one of them. The old 'pass-fail' binary, to which we grew up, was now replaced

by grades. Few simple expressions like A to Z, or 1 to 9 or percentages were easy for parental understanding; but some were so complex that I had to order 'Statistics for dummies' online. Percentile, Z score, and T values appeared in my sons 'scorecard', it had no semblance with the piece of paper, the 'marksheet' of yester years that I ferried between the school teacher and my parents, with numbers jotted in blue and mostly red.

HF also showed a sea change in concept, from binary of 'failure-no failure' to continuous variable. From simple NYHA class to Ejection fraction and NT-pro-BNP, the binary 'yes-no' changed to continuous variable. A Patient with NYHA class 2 symptoms, EF 55% and NT-pro-BNP 100 pg/ml would be judged to have an excellent prognosis, while one with NYHA class 4, EF 25% and NT-pro-BNP of 20,000 pg/ml would have a harsh sentence, given options of either being hooked on to an ICD or CRT for life or live with someone else's heart . A patient could fall anywhere in between these two extremes, and have outcomes somewhere in the sliding scale. For a while, this looked nice but problems cropped up when continuous variables failed to predict outcome in many subsets. A heart failure with preserved ejection fraction (HFpEF) with a normal EF and mildly elevated BNP and multiple comorbidities surprised us by throwing up a bad outcome, while patients with very high biomarkers, whose biomarker levels came down quickly in-hospital (wet BNP) did better than expected. Emergence of concepts of 'mid-range EF' took the sanity out of whatever was left.

Searching for Phenogroups

Like every chronic disease, HF also depends on genetics and environment. A susceptible genome, exposed to a specific environmental insult may show a specific defect, and that shows as a subset. Such subsets are not overtly predicted by a sliding-scale variable. Sliding scale model also does not predict therapy outcome reliably. Does the therapy need to be different with a person with Class 1 symptoms and EF of 25% with NT-pro-BNP of 3,000 from aclass 4 with EF of 40% and NT-pro-BNP of 20,000? The answer is, we don't know. An obese young diabetic HF patient with LVH, AF with EF55% is different from an elderly post MI HF with LVEF 30%. A subset created bypooling 'larger data' incorporating genotype, phenotype and therapy response, would tend to homogenise an 'individual subgroup' andbetter predict the outcome and response to therapy. Today's powerful analytic network and search-engines coupled to artificial intelligence can allow us to input such data to predict the outcome better. Most patients with such specific subset characters show minimal 'in-subset' variability and, more importantly, similar response to therapy. More characters assigned to a subset, more specific is likely to be their response to an individual therapy.

The Future

TOPCAT study (1) looked into the benefits of addition of spironolactone to Heart failure with preserved EF (HFpEF), and as we know, overall it turned out to be a negative trial. Recently, Cohen et al (2) took out the TOPCAT data and did an extensive analysis of genetic, and phenotypic data (49 key protein analytes – angiopoietins, Cystatins, MMPs, ANP, BNP etc) coupled with echocardiographic data (38 data-points). A complicated 'latent class analysis' (LCA) of this huge multi-layered data showed emergence of 3 distinct 'pheno-group' subsets.

The subset of those in middle age, with metabolic derangements like diabetes, more left ventricular hypertrophy (LVH), left atrial enlargement(LAE) and atrial fibrillation (AF) but normal arterial stiffness tended to have a worst outcome They, paradoxically, had the best response to spironolactone therapy. This subset

had higher inflammatory markers and a more active renin-angiotensin-aldosterone axis. In contrast, younger patients with no metabolic abnormality, no LVH, no LAE, no AF and normal arterial stiffness, had the best outcome. Data-driven, genotype, phenotypic subsets analysis seems to be the best in predicting outcome of HFpEF.

Park et al (3) recently published a large database of HF patients with a longitudinal follow up data of dynamic change of EF, coupled with global longitudinal strain (GLS). The study followed up 1130 patients of HFrEF and 975 cases of HFpEF.They were sub-grouped on whether or not EF remained same, improved (in case of HFrEF) or declined (in case of HFpEF). While improved EF (in HFrEF cases) hadthe best outcome (all cause 5-year mortality of 17%), declined EF in HFpEF fared the worst (all cause 5-year mortality of 43.1%). The trajectory of change of LVEF over time clearly predicted the long term outcome.

Defining subsets on genotype and phenotype incorporating large database, coupled with a dynamic change of parameters (predictive trajectory) seems to be the best way of prediction of HF outcome and treatment.
This year, USMLE decided to do away with "percentile, and go back to pass-fail; a continuous variable parameter did not seem to work out better than the binary.

A 'pass-fail' of a student early in career doesn't tell us much about his future academic endeavour. Even a sliding scale continuous variable parameter fail to make a precise prediction. A dyslexic student, excelling in abstract art, may fail the binary as well as any continuous variable scale of standard academics.

A heart failure patient with HFpEF with obesity and diabetes also would show a skewed parameter on a standard binary or a variable scale. A broader view of the problem, early triaging to a subset, based on large data-set, genetic, phenotypic, biochemical variables, coupled with a dynamic understanding of the trajectory is our best bet. That is the future of personalised care-to un-burden a school kid or a dilated, failing heart.

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Pediatric HF *vs* Adult HF
What is different?

Dr. Arun Gopalakrishnan
MD, DM
Assistant Professor of Cardiology
SCTIMST, Trivandrum, Kerala
Email: arungopalakrishnan99@gmail.com

Pediatric heart failure is a heterogeneous entity as opposed to heart failure in adults which is well characterized and backed by large scale clinical trials. Primary heart failure in children has been reported in 0.87 – 7.4 per 100,000 children, much lower than in adults. While coronary artery disease, lifestyle related issues of systemic hypertension, diabetes mellitus, dyslipidemia, obesity, and rheumatic heart disease account for the lion's share of heart failure in adults in India, congenital heart diseases and cardiomyopathies are the major causes of pediatric heart failure.

"Children are not miniature adults.

Adults are just outdated children."

(Dr Seuss)

Classification of Heart Failure

The New York Heart Association (NYHA) classification remains the most widely used clinical score for heart failure. This is based on the evaluation of four cardinal cardiovascular symptoms – shortness of breath, fatigue, palpitations and angina. While this may be applied to older children, analysis of heart failure in young children needs to incorporate other clinical variables specific to them – feed tolerance, growth, diaphoresis and peripheral perfusion. The Ross classification developed in 1987 incorporates some of these factors for application in infants and young children with heart failure. Subsequent modifications permit detailed analysis of age-based symptoms, but are often cumbersome.

Clinical Classification of Heart Failure

	New York Heart Association	Ross (Original)
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea	No limitation or symptoms
Class II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea.	Mild tachypnea or diaphoresis with feeding in infants, dyspnea at exertion in older children; no growth failure
Class III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.	Marked tachypnea or diaphoresis with feedings or exertion and prolonged feeding times with growth failure from CHF
Class IV	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.	Symptoms at rest, with tachypnea, retractions, grunting, or diaphoresis

Ross scoring system for heart failure in infants

	Score		
	0	**1**	**2**
Feeding history			
• Volume consumed per feeding (oz)	>3.5	2.5 – 3.5	<2.5
• Time taken per feeding (min)	<40	>40	-
Physical examination			
• Respiratory rate (per min)	<50	50 – 60	>60
• Heart rate (per min)	<160	160 – 170	>170
• Respiratory pattern	Normal	Abnormal	-
• Peripheral perfusion	Normal	Decreased	-
• S3 or diastolic rumble	Absent	Present	-
• Liver edge from right costal margin (cm)	<2	2 – 3	>3

Total score: 0–2 (no congestive heart failure (CHF)), 3–6 (mild CHF), 7–9 (moderate CHF), 10–12 (severe CHF)

Role of cardiac biomarkers

Natriuretic peptides are recommended for the diagnosis and evaluation of heart failure in adults and various cut-offs have been established for its identification and exclusion. While these markers may be used in children, the cut-offs are less well established and tend to vary with age. NT-proBNP is a good marker of clinical severity and worsening systolic function in children with heart failure and has a longer half-life than BNP. NT-proBNP levels are elevated in newborns, and should be checked only beyond day 4 of life. NT-proBNP levels have been noted to be lower in children below three years of life as opposed to older children. The median NT-proBNP in healthy children in the first month of life was reported to be 1360 pg/ml. The value decreased to 106 pg/ml in children aged 1 – 11 months. Age-stratified Ross classification of heart failure suggests a threshold of <450 pg/ml and <300 pg/ml to rule out heart failure in children below 3 years and older children respectively. The age-stratified version also allocates a score of 2 for NT-proBNP values >1700 pg/ml and >1500 pg/ml in children below 3 years and older children respectively. The PCM Biomarkers study is expected to shed light on application of natriuretic peptides in children with cardiomyopathy and heart failure.

Genetic testing is of primary importance in children with heart failure and cardiomyopathy. The yield for identifying a disease-causing gene variant is highest in children with hypertrophic cardiomyopathy and in those with a first-degree relative affected by a cardiomyopathy. Disease-causing mutations in pediatric dilated cardiomyopathy (DCM) are identified in <25%.

Pathophysiology and Treatment

The pathophysiology of heart failure in children also differs from that in adults. Adults with DCM have been identified to have down-regulation of only the β1-adrenergic receptors whereas pediatric patients have down-regulation of β1 and β2 receptors. Therefore, nonselective b-blockers, such as carvedilol, might cause a powerful adrenergic down regulation in children. Myocardial fibrosis and fibrotic gene expression is less often in children with DCM, unlike in adults. Consequently, anti-remodelling agents such as aldosterone antagonists, may not be as effective in pediatric heart failure.

An Elusive Case of Amyloidosis

Dr. Anoop George Alex
MD, DM,
Associate Professor,
Dept. of Cardiology, CMC Vellore
Email: alexanoop@gmail.com

Dr. Logesh MR
Senior PG RegistrarDept. of CardiologyCMC Vellore
Email: logesh.cardio@gmail.com

History:

48yr gentleman, with no comorbidities in past, presented with history of insidious onset dyspnea, worsened from NYHA II to NYHA IV over 8 months, associated with paroxysmal nocturnal dyspnea and orthopnea. It was also associated with exertional fatigue and exertional palpitations for 4 months and pedal edema for 3 months.

On Examination:

He had generalized muscle wasting, periorbital hyperpigmentation with ecchymosis around both eyes and macroglossia. JVP was elevated 10 cm from angle of Louis with prominent Y descent, apical impulse was at left 5th intercostal space on mid clavicular line, LVS3 was heard on auscultation with normal first and second heart sounds. Breath sound were decreased in right basal region.

ECG and CXR:

His electrocardiogram showed sinus rhythm, indeterminate axis with low voltage complexes on limb leads and poor progression of R waves on chest leads. His chest X-ray showed right sided pleural effusion and marked pulmonary venous congestion with normal sized heart.

Other investigations :

Complete blood count - normal, ESR- 44, RFT, LFT and Urine routine - normal, NTpro BNP - 13396, Urine BJP - positive, Beta 2 Microglobulin - 4.71, 24 hrs urinary protein - 310/1290, Immunofixation electrophoresis - Faint lamba +ve, Immunoglobulin - IGG - 990/ IGA -130/ IGM - 93, Serum electrophoresis - Paraprotein - negative(alb 3.2, total protein 5.3), Kappa - 26; Lamba - 457(markedly elevated) ; K/L - 0.059, Abdominal fat pad biopsy - Negative for amyloid, Rectal biopsy - No evidence for amyloid, Bone marrow - Mildly hyper cellular marrow with trilineate hematopoiesis, no abnormal cells; no evidence of amyloid deposition.

Figure 1: Showing generalised muscle wasting, peri orbital hyperpigmentation with ecchymosis around both eyes and macroglossia

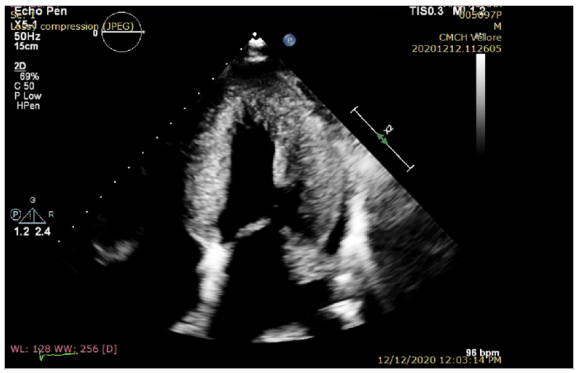


Figure 2: Showing thickened LV wall with speckled appearance of myocardium on echo cardiography

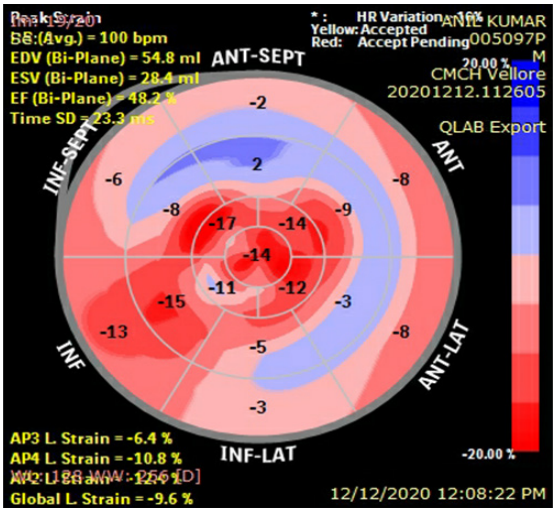


Figure 3: Showing Apical sparing on GLS (Cherry on top appearance)

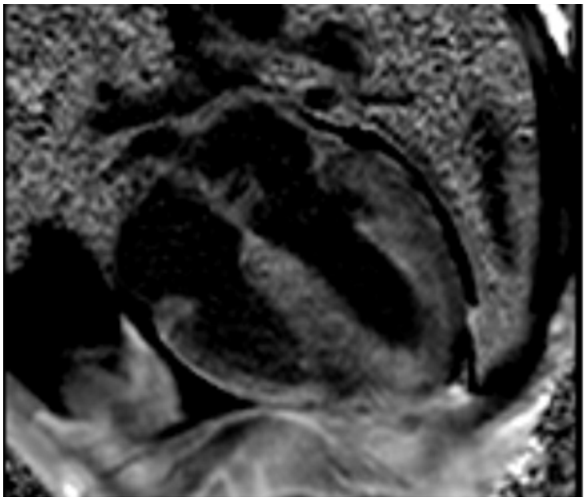


Figure 4: Four chamber post gadolinium 10 minutes PSIR image showing thickening of LV and RV myocardium with late gadolinium enhancement predominantly in the subendocardial region.

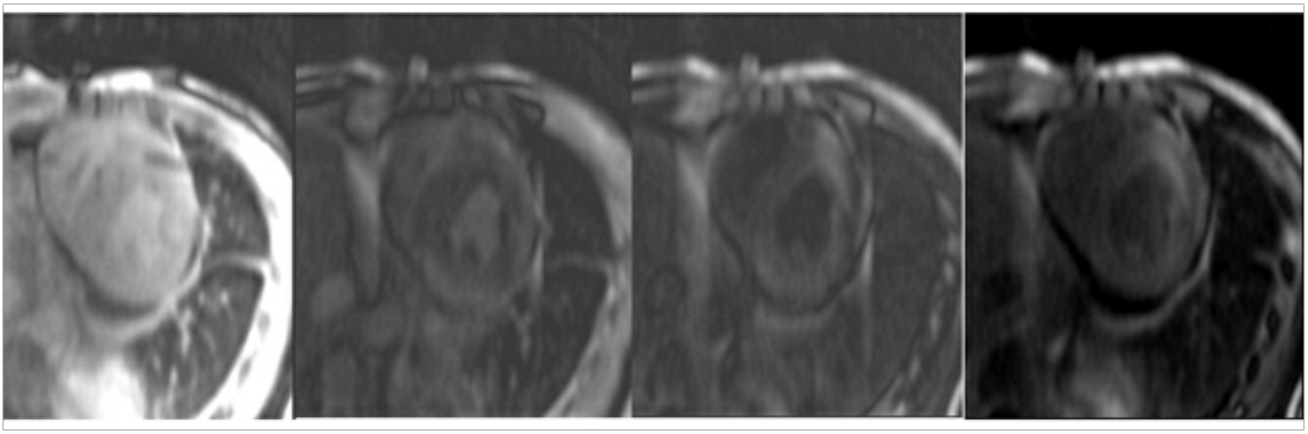


Figure 5: Serial T1 scout image in short axis view after IV gadolinium injection, with progressively increasing inversion times from left to right, showing reversal of nulling pattern, with myocardium nulling first before blood.

Even though there was no tissue diagnosis of amyloid, he was started on chemotherapy (Cybor D regimen) in view of classical echocardiographic and cardiac MRI features of amyloidosis.The patient is currently on follow up.

Crossword of a Different Kind

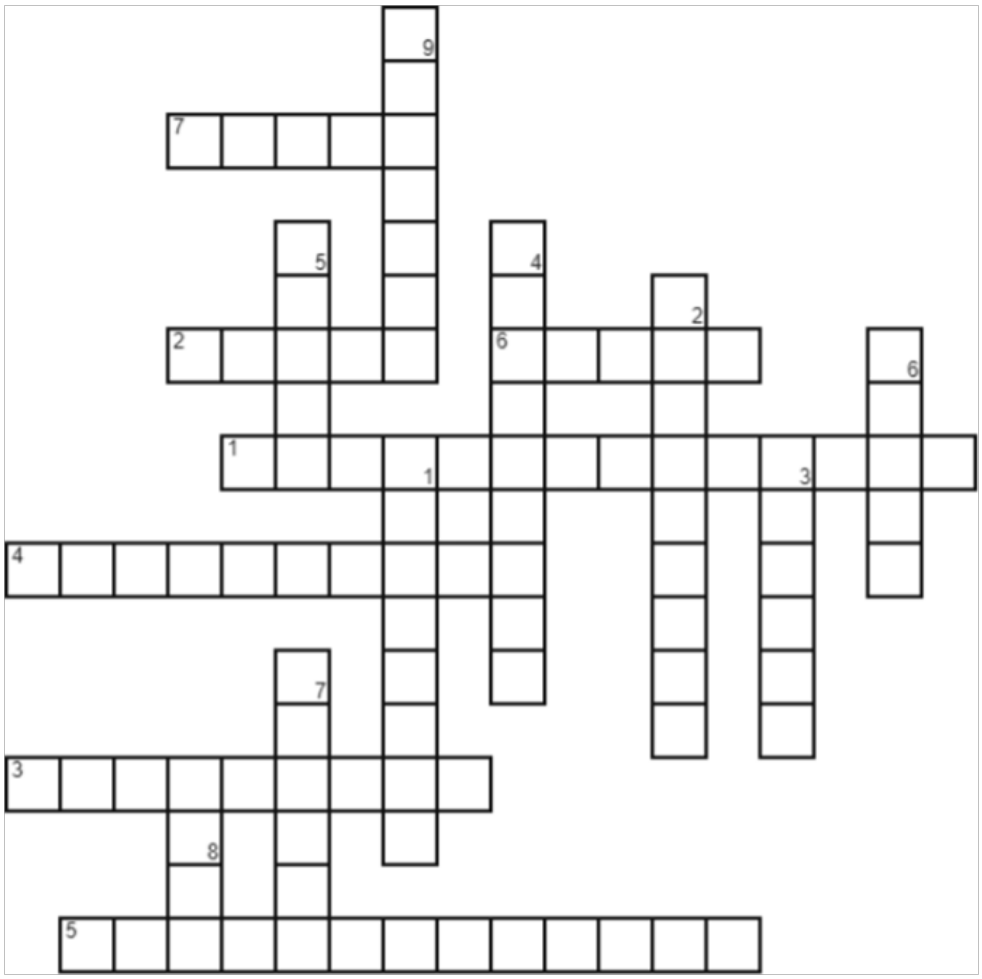
Dr. Praveen S
MD, DM
Associate Professor
Department of Cardiology
Government Medical College
Trivandrum, Kerala
Email: praveensatheesan@gmail.com

TRIAL NAMES OR GAMES ?

Clinical trials dates back to 562 BC when King Nebuchadnezzar II tested a meat based diet against vegetable diet among his people.But it was Dr James Lind who started off in 1747 with his trial on sailors with scurvy.Over the years trials have become a necessity for medical speciality to grow and progress.

Clinical trials are assigned names for easy recognition, but nowadays they have become more and more confusing .The field of cardiology is also not far behind in this context with an array of trials. Trials have been named with straight forward acronyms like PURE study (Prospective Urban Rural Epidemiology),ISIS(International Study of Infarct Survival) as well as fascinating names like the CASABLANCA trial(Catheter Sampled Blood Archive in Cardiovascular Diseases) and the TORPEDO study (Treatment of cardiovascular Risk in Primary care using Electronic Decision support).The naming of trials have become more intriguing and complex these days and we have five to six trials with the same name eg: HOPE trial.When googled, we have a TORPEDO study in rheumatoid arthritis ,oncology, in cardiovascular area, one in primary care and another one in deep vein thrombosis. Remembering the trial names for the exams have become a verbal jugglery for the students.

Here we have a crossword with names of clinical trials related to heart failure. The trials included could be a positive trial or a negative one. So happy Crosswording.



ACROSS

1. Heart safety vs Sugar control consequence
2. Fit together as Alfieri
3. Ferric Carboxymaltose on Performance
4. The Sun and the Center of the Beta blocker world
5. Largest Cardiovascular outcome trial to date with a diabetic drug
6. Abnormal Lung Sounds
7. Mortality reduction of Enalapril answered

DOWN

1. Recombinant Human B-type natriuretic peptide stepped up
2. Seeing flashes of Colour are……..
3. For Oil painting a diabetic
4. Ultrafiltration in Heart failure fondled
5. Alternative , Added and Preserved versions
6. Choice of Betablocker is celestial
7. Statin in Heart failure crown
8. Betablocker for big heart
9. Shock vs Drug contest

How Many did you get Right?

Turn the page and see...

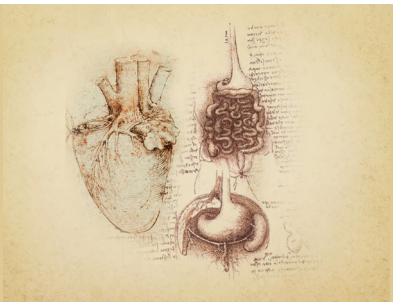
Crossword Key

ACROSS

1. EMPAREG OUTCOME
2. COAPT
3. CONFIRM HF
4. COPERNICUS
5. DECLARE TIMI 58
6. RALES
7. SOLVD

DOWN

1. ASCEND HF
2. BEAUTIFUL
3. CANVAS
4. CARRESS HF
5. CHARM
6. COMET
7. CORONA
8. MDC
9. SCDHEFT



Cover image:

Anatomical drawings of the heart and gut by Leonardo da Vinci (1452 - 1519)

We would love to hear from you !

Please send your comments, suggestions and scientific contributions to **hfaioffice@gmail.com**

or scan QR code

Office Address:
Room Number 1212, Medical Block, 2nd Floor
Department of Cardiology
Sree Chitra Tirunal Institute for Medical Sciences and Technology
Medical College Campus, Trivandrum, Kerala-695011

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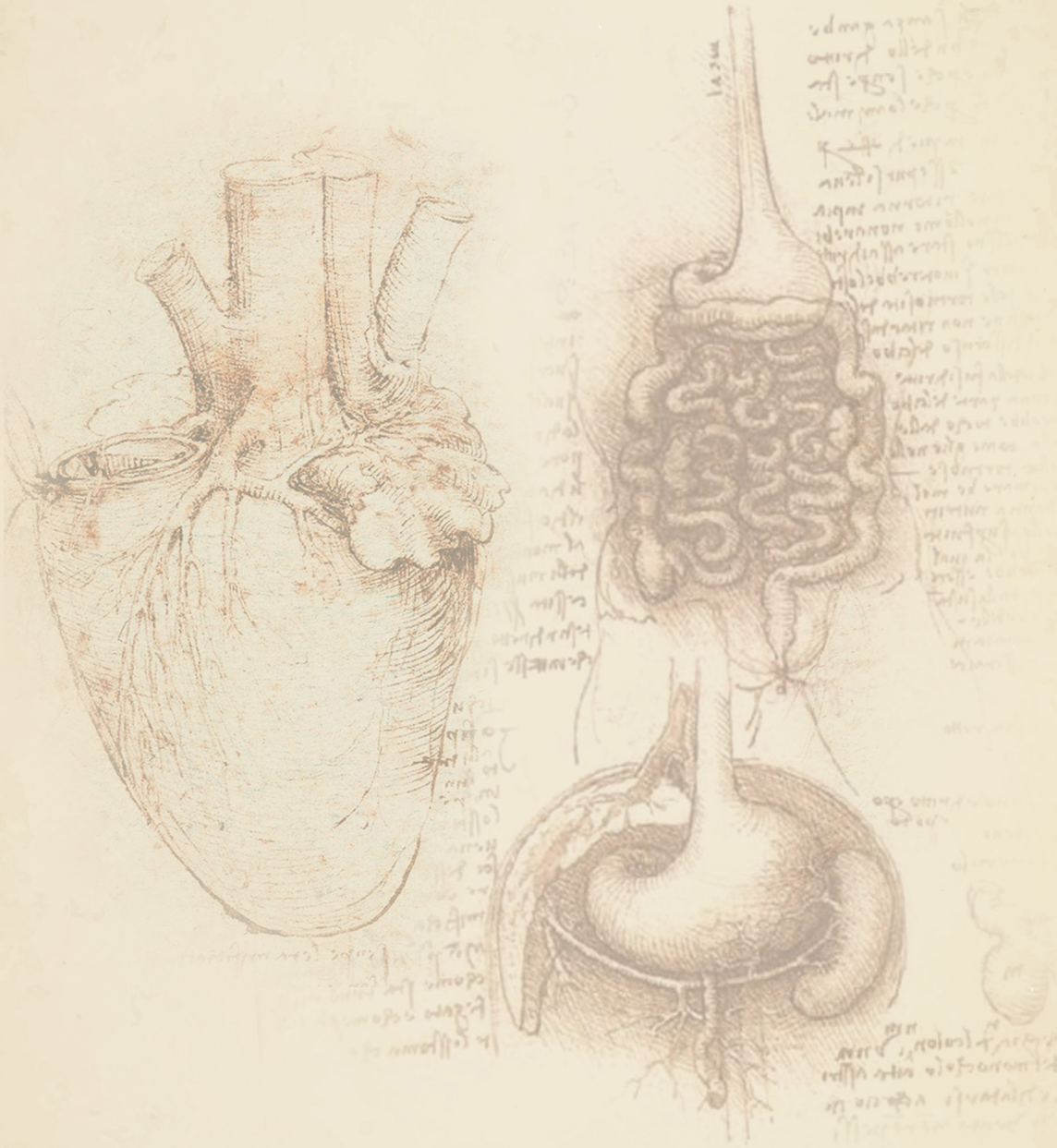
Notes:

HEART FAILURE REWIND



HEART FAILURE ASSOCIATION OF INDIA

Improving Heart Failure Care