NEWSLETTER
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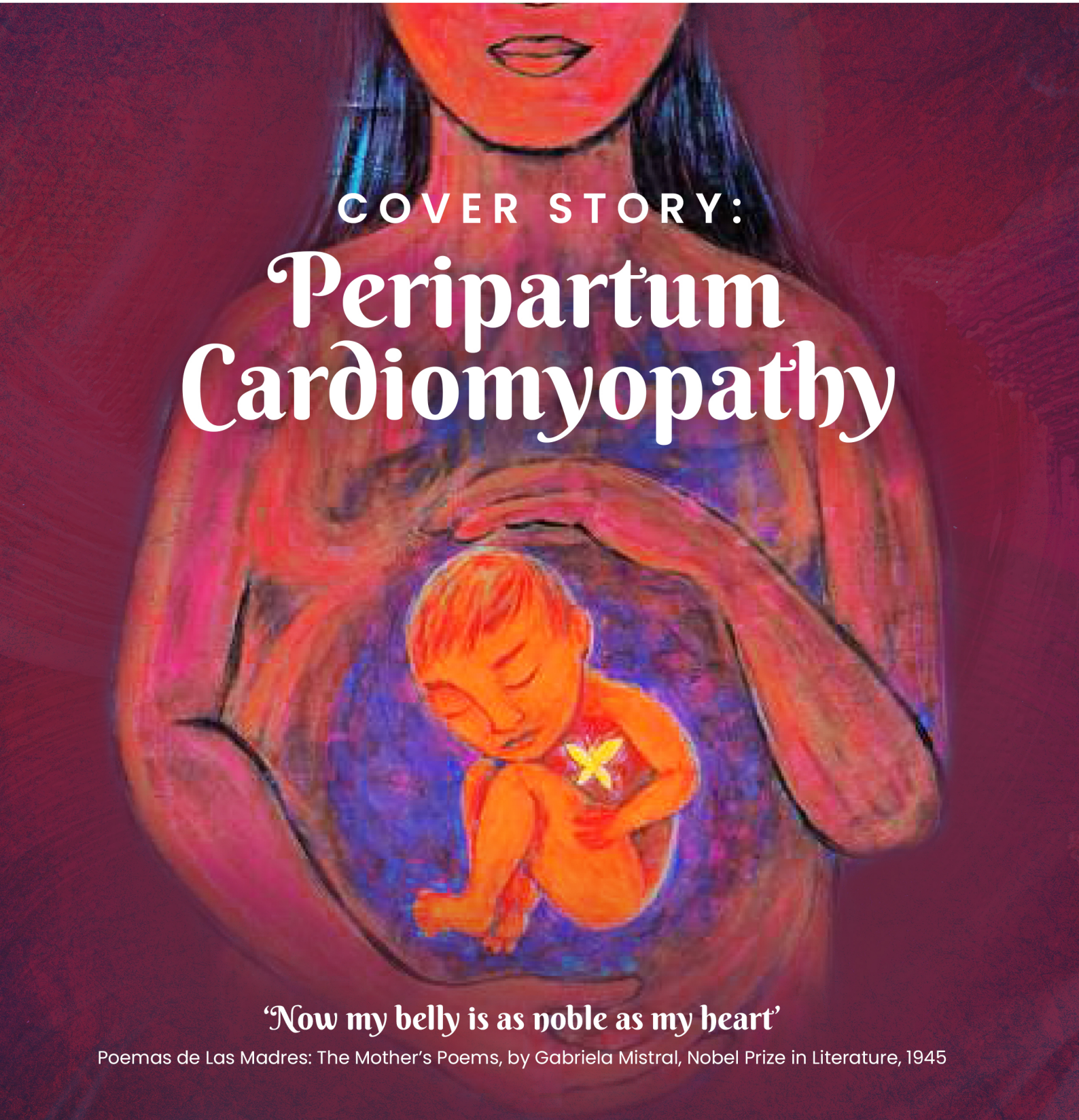
HEART FAILURE ASSOCIATION OF INDIA
Improving Heart Failure Care

HEART FAILURE REWIND



COVER STORY:

Peripartum Cardiomyopathy

'Now my belly is as noble as my heart'

Poemas de Las Madres: The Mother's Poems, by Gabriela Mistral, Nobel Prize in Literature, 1945

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Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a form of dilated cardiomyopathy (DCM), in which previously healthy women present with heart failure due to left ventricular (LV) dysfunction during the last months of pregnancy or up to 5 months after delivery. Worldwide, the disease affects approximately 1 in 1000 pregnancies, however its prevalence differs significantly between different regions and ethnicities.

Clinical presentation and differential diagnosis

Non-specific symptoms are common during or after pregnancy, and frequently lead to a contact with a medical professional. It can be very challenging to distinguish PPCM from the normal physiological changes of pregnancy and the postpartum period or to differentiate the condition from a pre-existing cardiac disease, which was aggravated during the pregnancy. Therefore, the diagnosis of PPCM requires a high index of suspicion.

The most common presenting symptoms of PPCM include dyspnea, orthopnea, paroxysmal nocturnal dyspnea (PND), fatigue or cough. History taking should be followed by a thorough clinical examination. Tachypnea, tachycardia and hypo- or hypertension are non-specific signs of heart failure, whereas jugular venous distension, a third heart sound and respiratory crackles are more specific to an underlying cardiac cause. However, in women with PPCM, conventional signs of heart failure are often not present and the condition cannot be ruled out due to absence of clinical signs.

When diagnosing PPCM frequent differential diagnoses have to be considered. The differential diagnoses differ according to whether a patient presents during or after pregnancy. These include hypertensive disorders of pregnancy, pregnancy-related complications such as pulmonary embolism or amniotic fluid embolism or a pre-existing cardiac condition. Moreover, non-cardiac conditions such as a respiratory disease, anemia, sepsis or renal disease should be excluded. When a cardiac dysfunction has been confirmed by echocardiography an underlying cardiac cause becomes more likely. However, PPCM has to be differentiated from other causes of heart failure such as (pre-existing) DCM, valvular heart disease (VHD), drug-induced cardiomyopathy (including chemotherapy-induced cardiomyopathy), congenital heart disease, Takotsubo syndrome, hypertensive heart disease, or myocarditis.

A detailed medical history is crucial to differentiate PPCM from other underlying causes. Any woman with signs or symptoms suggestive of PPCM should undergo urgent cardiac investigation. The basic work-up should include electrocardiography, laboratory tests including natriuretic peptides, chest radiography and echocardiography (Figure 1).

Electrocardiography (ECG)

The ECG is a powerful diagnostic tool in the work-up of cardiac disease. It is inexpensive and widely available, even in healthcare centres with limited resources. Therefore, it should be considered as a basis of clinical work-up in all women with a potentially cardiac-related complaint, particularly in those with a suspected PPCM. It has been shown that ECG abnormalities are present in up to 96% of women with PPCM. However, there are no ECG features that are specific and diagnostic of PPCM. The 12-lead ECG often finds sinus tachycardia, a narrow QRS complex, widespread T wave inversion, and a prolonged corrected QT (QTc) interval (Figure 2). Sinus tachycardia and a prolonged corrected QT interval (QTc >460ms) are associated with adverse outcomes at 6 and 12 months, respectively.

Natriuretic peptides

Contemporary heart failure guidelines recommend natriuretic peptides as the biomarker of choice in the diagnostic work-up of patients with heart failure. If available, they should be measured in women with suspected PPCM. For PPCM, a threshold of < 100 pg/ml for BNP and < 300 pg/ml for NT-proBNP was proposed to rule out heart failure during pregnancy or the postpartum period. NT-proBNP levels in PPCM are typically higher than during normal pregnancy and healthy postpartum period, and those reported for women with pre-eclampsia. Recently, a baseline NT-proBNP ≥ 900 pg/ml has been shown to be a predictor of failure to recover LV dimensions and systolic function within one year in a South African cohort.

Chest radiography

The chest radiography is helpful to exclude other causes for dyspnea such as infection, effusion, or pneumothorax. In case of PPCM it may show an increased cardiothoracic ratio, with signs of pulmonary congestion or effusion, however, it can also be normal.

Transthoracic echocardiography

The diagnosis of PPCM is confirmed by echocardiography, which typically shows a dilated LV with impaired systolic function (i.e., LVEF < 45%) at time of diagnosis. Coexisting functional mitral regurgitation and right ventricular dysfunction are common ancillary findings (Figure 3). A comprehensive right heart assessment is recommended as it has been shown to be an independent predictor of poor prognosis.

Treatment

Therapeutic management of acute PPCM differs depending on the severity of heart failure and whether the patient presents during the antepartum or postpartum period. For women presenting during pregnancy, joint cardiac and obstetric care is recommended. Treatment should be in accordance to the European Society of Cardiology (ESC) guidelines for the management of cardiovascular diseases in pregnancy. During pregnancy treatment options are limited, as angiotensin-converting enzyme (ACE-) inhibitors, angiotensin receptor blockers (ARBs) mineralocorticoid receptor antagonists (MRAs) are contraindicated because of concerns of teratogenicity and fetotoxicity. Hydralazine, nitrates, beta-blockers, and diuretics can be used in pregnancy instead. Diuretics should be considered, if patients are symptomatic or show signs of congestion despite concerns about decreased placental blood flow. Although beta-blockers have an increased risk of fetal growth restriction, they should be administered in all stable patients with a preference for metoprolol.

Postpartum women should be treated in accordance with contemporary heart failure guidelines (i.e., treatment should consist of combination of beta-blockers, ACE inhibitors/ARBs, MRA, and diuretics). The addition of the dopamine-D2-receptor agonist bromocriptine has been shown to promote LV recovery and clinical outcome in women with severe PPCM. It is recommended to prescribe anticoagulation when bromocriptine is administered, due to concerns of an increased thromboembolic risk. As high resting heart rate has been shown to be a predictor of adverse outcome, treatment with ivabradine should be considered in patients with sinus rhythm with a resting heart rate > 70 beats per minute, despite of a maximally tolerated beta-blocker dose. The essential treatment for acute PPCM can be summarized with the acronym "BOARD": **B**romocriptine, **O**ral heart failure therapies, **A**nticoagulants, vaso**R**elaxing agents, and **D**iuretics (Figure 1).

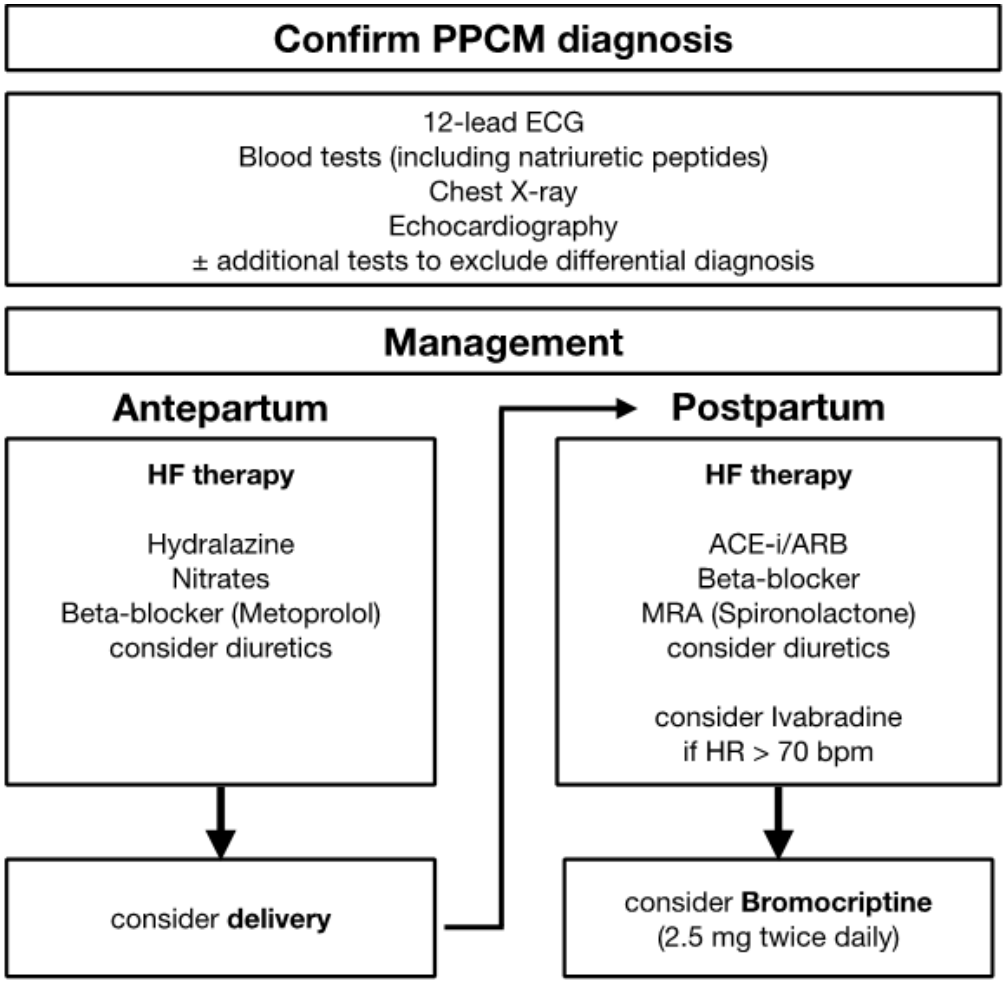

Figure 1: Diagnosis and management of peripartum cardiomyopathy. ECG: electrocardiography, HF: heart failure; angiotensin-converting enzyme (ACE-) inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist. Adapted from Bauersachs J, Arrigo M, Hilfiker-Kleiner D, Veltmann C, Coats AJS, Crespo-Leiro MG, et al. Current management of patients with severe acute peripartum cardiomyopathy: practical guidance from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. Eur J Heart Fail 2016;18(9):1096–105.

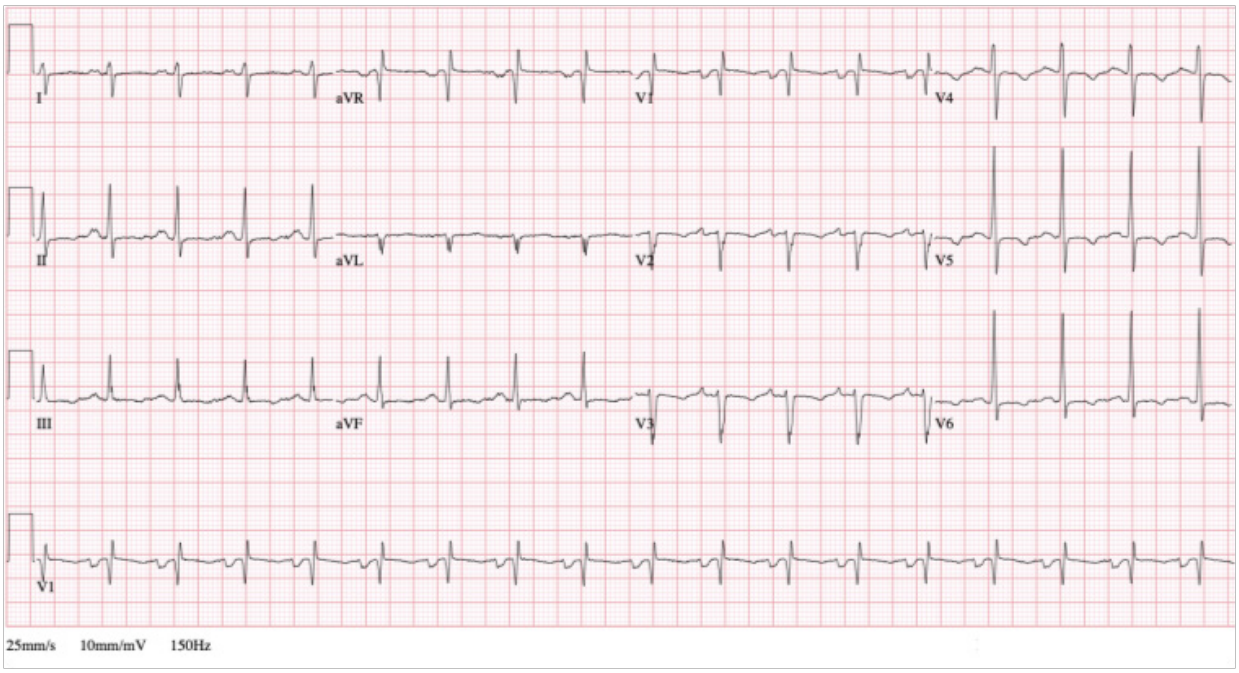

Figure 2: A 12-lead ECG of a patient with PPCM. It shows sinus tachycardia (ventricular rate of 106), with evidence of left atrial enlargement (bifid wide P wave in standard lead II and terminal negativity in V1). The QRS complex is narrow and has a slightly rightward axis (100 degrees). There is fractionation of the QRS in leads III, aVL, V2, and V3 and T-wave inversion in V3–V6. The QTc interval is prolonged (QTc 494 ms).

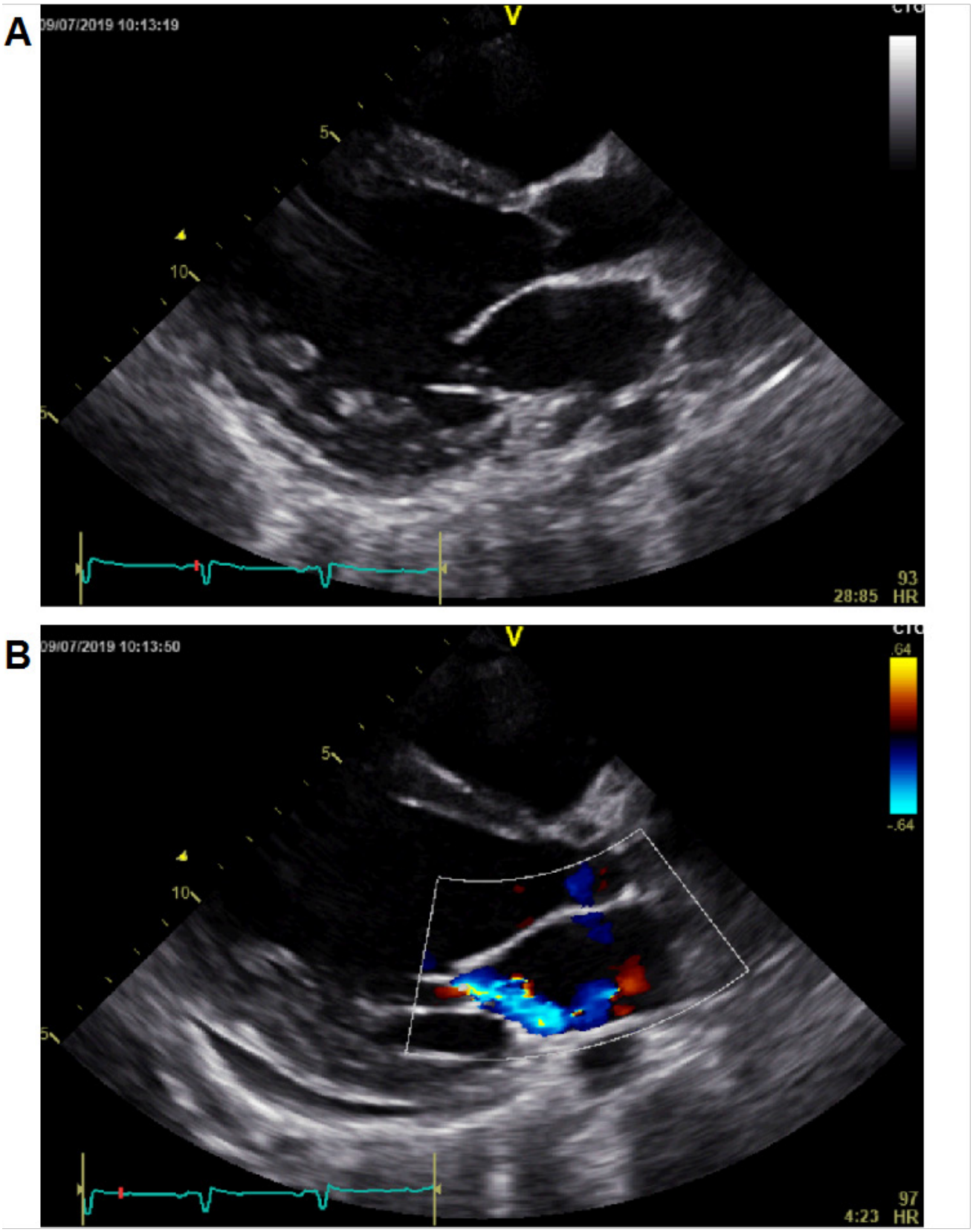

Figure 3: Transthoracic echocardiography of a patient with peripartum cardiomyopathy. Parasternal long axis (PLAX) view showed (A) a dilated left ventricle (LV) with poor systolic function (B) and secondary mitral regurgitation on colour flow Doppler.

Freebie From New York

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Historically, human dwellings were built on fertile land, close to fresh water sources, for easy procurement of the must-have ingredients needed for survival. As number of settlers increased; the need to have some basic tenets of housing evolved in each cluster. Random rural settlements gave way to stringent urban laws. The beauty of rustic living transformed into stale geometry of brick and mortar. Instead of roads connecting homes, dwelling apartments now had to be built around carefully planned grid architecture.

Manhattan was one of those early adopters. In 1811, the city commissioners transected the landmass with 12 avenues and 155 streets, allotting 20 blocks to a mile. This meant that every block was approximately 270 meters in length and 80 meters in breadth. Presently there are roughly 2,800 blocks in New York City.

Adjectives are confusing; terms like small and big, little or huge; it depends on the speaker's perspective. Over time, the need to qualify everything by numbers, measures, weights, including data, became inevitable for clarity.

But biology posed a different ballgame altogether. The challenge of quantifying human suffering, pain, breathlessness, fatigue, is not easy. A grey scale of depression bringing in dark clouds of suicide or a Richter scale of anxiety ready to break into a quake of panic is not easy to develop and apply.

In 1928, the New York Heart association (NYHA) proposed a classification depending on how much a patient of cardiac disease could walk without symptoms. The city-blocks provided an easy reference which the patients could easily relate.

'How many blocks could you walk without getting breathless' a logical question; evolved slowly into a more official 'standardized' NYHA class.

A person who could walk 2 blocks (80 meters X 2) without a symptom was classified as 'class 1', one who could complete with symptoms as 'class 2'. On who had to stop short of two blocks, was labelled 'class 3' and one who could not take a decent start was 'class 4'.

Over time NYHA class has become the most common medical expression of portraying a clinical symptom-status of a cardiac patient.

But as newer planned cities sprang up, city block dimensions changed. Chicago decided to adopt a 16 block-a-mile grid, which became popular worldwide. But physicians stuck on to their allegiance to New York. Canadian cardiovascular society (CCS) is a distant second contender. Over the last hundred years, medical technology has totally transformed; from stethoscope to hand-held ultrasound, from heparin to primary angioplasty; but medical students and consultants still start their case presentation with the ubiquitous NYHA class.

From the icy Alaska to the humid Zambia, and everywhere in between, NYHA class informs physicians regarding symptomatic status, therapy decisions and long-term prognosis, reliably. An echo may show a preserved ejection fraction, a biomarker may be falsely low, a NYHA class is still a simple clinical tool to estimate survival in HF.

The grid of Manhattan, the brick & mortar of New York has cast an unfailing spell on an unpredictable, fragile, failing human heart.

Urine Na in Acute Heart Failure: Time to Go with the Flow?

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Continue the medicine until the urine flows.
Let the medicine therefore be continued, until it either acts on the kidneys...

William Withering, from 'An Account of the Foxglove and Some of its Medical Uses, with Practical Remarks on the Dropsy, and some other diseases', 1785

Of Congestion, Kidneys and the Failing Heart

Congestion is a hallmark of acute decompensated heart failure (ADHF). The kidneys, being the master regulators of fluid and salt balance, play a pivotal role in the process, so much so that heart failure is often as much a renal disease as it is a cardiac one. It therefore is not surprising that the most important group of drugs used in initial management of ADHF - the diuretics, act primarily on the kidneys, and not the heart!

Diuretics in Acute Heart Failure

In acute heart failure, there is rapid onset or worsening of symptoms and/or signs of HF. There is volume overload, with sodium and water retention in the extracellular space. The cornerstone of initial treatment is diuretic therapy, most commonly with loop diuretics like frusemide or torsemide. Diuretics exhibit a dichotomy in their action, with dual effects of diuresis and natriuresis. Whatever may be the predominant effect, there is no doubt regarding the merits of early, effective decongestion, with sodium and water elimination leading to reduced extracellular fluid volume and attainment of euvolemia. Apart from early symptom relief, this contributes to lower in-hospital mortality, improved survival and lower re-hospitalization rates.

Concept and Rationale for Urine Sodium Assessment

Conventional assessment of congestion/ euvolemia and tailoring of loop diuretics is a dynamic process, incorporating one or more of clinical, echocardiographic, biomarker, chest X ray, lung ultrasonography and biochemical variables. Diuretic response assessment based on fluid balance, urine output and weight changes has flipsides, being difficult, sometimes inaccurate, very often incomplete, mostly non-standardized and of course, delayed. Herein lies the new value proposition of urinary sodium (U Na) measurement, with utility in assessing diuretic response, detecting diuretic resistance early, adapting therapy, risk stratifying patients with ADHF and helping in prognostication.

In a nutshell, in a patient with acute HF, a few hours after initial diuretic therapy guided by fluid based metrics, if the Spot U Na is high and above a particular threshold value (usually > 60 mmol/l, range 50-70 mmol/l), it indicates effective decongestion and a favourable outcome. On the other hand, if the U Na is low and below a particular threshold value, it indicates insufficient diuretic response, persistent congestion and implies a risk of worsening HF and portends a higher mortality.[1] Early natriuresis as determined by Urine Spot Na may thus predict subsequent diuresis.

Evidence base

Urine Na estimation in the setting of HF has been studied in the in-hospital or Intensive Care Unit (ICU) setting, emergency room (ER) setting and in ambulatory or out-patient (OP) setting. Various diuretics including intravenous bolus and infusions of frusemide, intravenous bumetanide and spironolactone have been studied. U Na has been linked to general outcome measures (mortality, re-hospitalisation, need for mechanical circulatory support or inotropes, worsening HF, length of stay) and specific outcome measures (urine output, weight loss, NT pro BNP, neurohormonal activation, tubular injury). Serial monitoring of weekly, pre diuretic first void morning U Na has been found to be useful in detecting a drop in U Na 1 week before an incident decompensation in ambulatory out-patients with chronic HF.

Status

Urine Na is now evolving as a biomarker in heart failure. *The 2019 Position Statement on the Use of Diuretics in Heart Failure with Congestion by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) incorporates U Na in its algorithm.*[2] On Day 1 of acute HF, after initial intravenous loop diuretic therapy and emptying of the bladder, a U spot Na at 2 hours of < 50-70 mmol/l and a urine output at 6 hours of < 100-150 ml/hour indicates insufficient diuretic response and calls for stepped pharmacologic therapy with early intensification of loop diuretics and/or sequential nephron blockade. On Day 2, if the 24 hour urine output is <3-4 L/day, the loop diuretic dose can be doubled and the response reassessed after 6 hours. If the response is suboptimal despite maximal dose (400-600 mg of frusemide), consideration should be given to the addition of thiazides/metolazone, acetazolamide/amiloride and/or SGLT2 inhibitors (Fig 1).

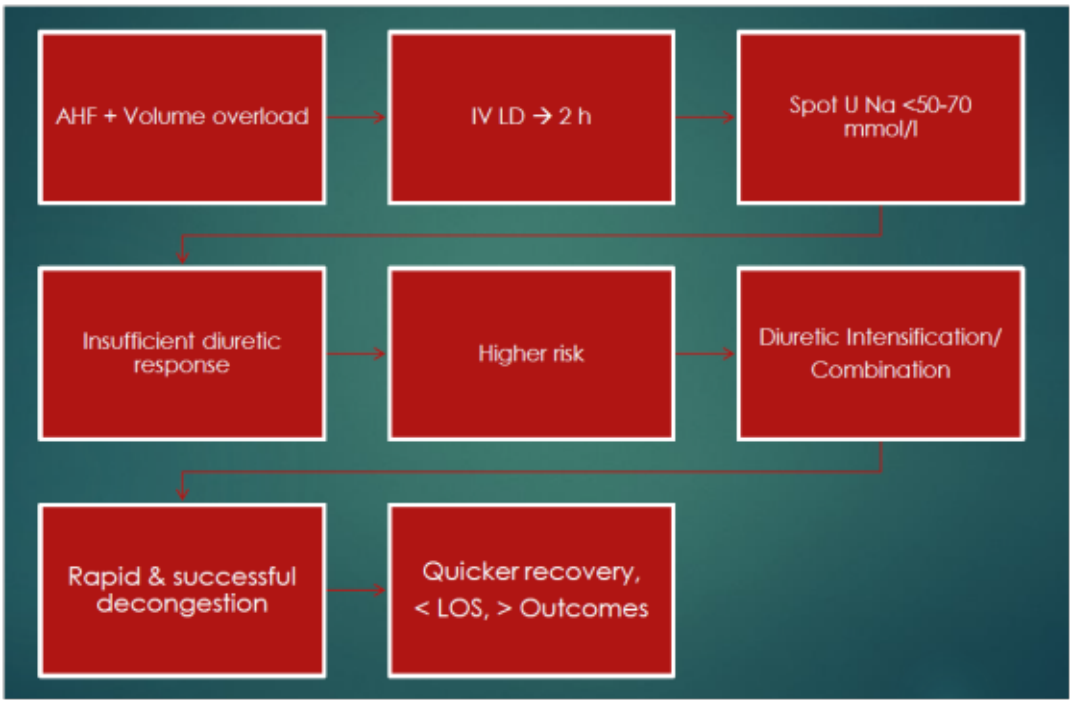

Fig 1: Role of Urine Spot Na. AHF: Acute Heart Failure. IV LD: Intravenous Loop Diuretic, LOS: Length of Stay

Advantages

Urine spot Na estimation is easy to do, widely available, inexpensive and can be done in ambulatory setting too.

Pitfalls

Variability can be due to renal dysfunction, prior diuretic usage, gender and ethnic differences and due to practical difficulties in the collection and assay. In addition, factors lowering urine volume (non osmotic vasopressin release, reduced fluid intake, acute kidney injury), factors increasing urine volume (glycosuria, excess dietary salt and water), metabolic alkalosis, bicarbonaturia, neurohormonal activation and the severity of heart failure might confound the results.

What does the Future Hold?

The ideal threshold value of Urine Na that would raise clinical concern or provide reassurance is yet to be clearly established. The elevation of the concept 'from association to causality' would require randomised controlled trials (RCTs) comparing optimization of diuretic therapy with traditional fluid based metrics to urine Na profile driven protocols.

Conclusion

Urinary Spot Na estimation in acute heart failure is conceptually appealing, practically feasible and has sufficient evidence base. Therefore, its role in assessing diuretic response, detecting diuretic resistance, guiding therapy, and also in risk stratification or prognostication is definitely worth exploring as part of a comprehensive and systematic approach to heart failure care. As is the case during the clinical use of any 'new' tool, understanding the strengths as well as the limitations is of utmost importance, always keeping the patient at the centre of the decision making process, taking care not to miss the forest for the trees!

Suggested Reading

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Heart Failure with recovered Ejection Fraction

More questions than answers!!

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10 – 40 % of patients with Heart Failure with reduced ejection fraction (HFrEF) can have complete (EF > 50%) or partial (EF : 40-50%) normalization of LV EF. Given the complexity and heterogeneity of this subgroup of patients, there is a lack of consensus on the definition, diagnosis, and management of this patient population.

Q: What is the accepted terminology for HFrEF patients with an improvement in EF?

There is no universally accepted terminology and many terms like 'HF with improved EF' have been used in this context. To avoid ambiguity in nomenclature, a JACC Expert panel recently proposed that these patients may be referred as Heart Failure with recovered EF, or HFrecEF.1 This is to denote that they were initially HF patients with a remodeled (eg: dilated) left ventricle and thus avoids confusing these patients with HF with preserved Ejection Fraction (HFpEF) , as well as with patients with a mid range LVEF (HFmrEF) (EF - 40% to 50%)

Q: Is there a definition for HFrecEF?

The following working definition of HFrecEF has been proposed by the JACC expert panel :

1) Documentation of a decreased LVEF < 40% at baseline
2) ≥ 10 % absolute increase in LVEF
3) A second measurement of LV EF ≥ 40 %

Measurement of the changes in LVEF should be obtained at least 3 to 6 months after the baseline LVEF, when the patient is stable hemodynamically, to avoid acute changes in LVEF that are secondary to changes in heart rate or loading conditions. These improvements in LVEF are typically accompanied by a reduction in LV volumes.

Q: Is there an overlap of HFrecEF with HFpEF and HFmrEF?

HFrecEF represents a clinical entity distinct from HFpEF and HFmrEF. Cases of HFrecEF in which there has been a modest recovery of LV function, with resultant EF between 40%-50%, can make differentiation from HFmrEf very difficult. Here lies the importance of prior documentation of LV EF for making the right diagnosis. So without the knowledge of the LV EF trajectory, HFmrEF patients should not be considered synonymous with HFrecEF patients.

Q: What really happens in HFrecEF? What is the biology behind recovery of ventricular function?

Improvements in LVEF are associated with a reciprocal decrease in LV end-diastolic volume, which has been referred to as reverse LV remodelling. Cardiac remodelling is a dynamic process, that occurs in a competing bidirectional manner - forward (pathologic) and reverse (beneficial). Reverse LV remodelling refers to the restoration of more normal cardiac myocyte size and LV chamber geometry, resulting in a leftward shift of the end-diastolic pressure volume relationship toward normal values. This also results in improved myocyte and LV chamber contractility. But it has been shown that many of the multilevel molecular changes that occur during forward LV remodelling remain dysregulated in reverse remodelled hearts, despite improvements in structural and functional abnormalities.2

Q. Can we predict which subsets of patients with HFrEF are more likely to have reverse LV remodelling and an improvement in EF?

Studies have shown that following subsets of patients are more likely to demonstrate an improvement in EF.3

Clinical parameters: Non ischemic aetiology, lower duration of HF, younger age, female sex, fewer co-morbidities, no LBBB

Genetic factors: Pathogenic gene variants not involving structural cytoskeletal proteins or Z-disk proteins

Echocardiography/CMR imaging: Greater contractility on strain imaging, absence of late gadolinium enhancement

Biomarkers: Lower levels of biomarkers (NT-proBNP, Troponin, sST2, Galectin-3 etc)

Among the different neurohormonal antagonists used in GDMT of HFrEF, beta blockers are most strongly associated with reverse LV remodelling. Although there is substantial evidence that ACE inhibitors and ARBs prevents forward LV remodelling, the evidence for regression of established LV remodelling is less definitive for them, but evidence do exist for ARBs. More recently, treatment with sacubitril/valsartan was shown to induce reverse LV remodelling and improve LV function in patients with HFrEF.4-6

Q. What is the natural history of HFrecEF? Is it very different from that of HFpEF and HFrEF?

Patients with HFrecEF have a significant decrease in HF hospitalization and improved survival compared to HFpEF and HFrEF (up to 50% in some studies)7. But after the initial improvement, a significant proportion of HFrecEF patients develop recurrence of LV dysfunction accompanied by recurrent HF events. One plausible explanation for this is that reverse remodelled hearts retain many of the molecular features of the failing heart. In fact, reverse LV remodelling represents a transition to a new, less pathological "steady state" that allows the heart to maintain LV pump function under normal conditions. However, this adaptation has less biological and contractile reserve capacity, and is therefore more prone to redevelop LV dysfunction in response to hemodynamic, neurohormonal, or environmental stress.

Q. What are the caveats in clinical assessment and follow up of patients with HFrecEF?

Symptomatology, Clinical examination and ECG:

Signs of volume overload are of particular concern in patients with HFrecEF. Patients who still require loop diuretics for symptom relief may represent a high-risk population, who are at risk of recurrent HF events.

If ECG changes like LBBB, repolarization abnormalities are still present, it can be assumed that myocardial disease is still present.

It has been suggested that once patients with HFrecEF are deemed "stable" for at least 1 year, they should be seen in outpatient clinic every 6 months for at least 3 years, then at least every year, due to the risk of relapse.

Biomarkers:

Biomarkers, especially NT-proBNP is useful for serial monitoring to detect early warning signs of relapse. It is recommended that biomarker assay should be done every 6 months until 12-18 months of recovery and then every 6-12 months.

2D Echo with Strain Rate imaging:

Despite improvements in gross myocardial functioning, global longitudinal strain and diastolic function rarely normalize in HFrecEF.8 However, among HFrecEF patients, higher global longitudinal strain (e.g: >16% absolute global longitudinal strain) is associated with stability of LVEF over short-term follow-up (2 years).

Echo evaluation should be at least done every 6 months until 12-18 months of recovery and then every 1-3 years.

Cardiac MRI:

CMR is best utilized to characterize the myocardial substrate at the time of de novo diagnosis of HFrEF, to provide valuable insights into aetiology of HFrEF. The utility of CMR, after some degree of LV remodelling or recovery has occurred, is largely unknown. However, it is suggested that CMR can be done after 1 year of clinically stable HFrecEF, if it has not been already performed at the initial diagnosis of HFrEF.

Q. Can we consider stopping GDMT in HFrecEF?

TRED-HF (Withdrawal of Pharmacological Treatment for Heart Failure in Patients With Recovered Dilated Cardiomyopathy) trial was the only randomized study which tested the hypothesis that GDMT could be withdrawn in asymptomatic HFrecEF patients. After screening 936 patients, 51 patients were randomized to either a phased withdrawal protocol of the HF GDMT or continued therapy with GDMT. Interstingly, the participants initially randomized to continued therapy also had their medications weaned. Within 6 months, as many as 44% of the withdrawal group and 36% from the second group experienced a recurrence of HF.9 Multiple clinical reports have also noted recurrence of LV systolic dysfunction once GDMT is stopped. Hence, based on the available data, it is recommended that GDMT should be continued in patients with HFrecEF.

Cessation of diuretic agents is encouraged among recovered-EF patient, and indeed, the ability to tolerate the lack of diuretics may be indicative of a lower risk of recrudescent HF in HFrecEF. If a patient with HFrecEF continues to require diuretics, then further titration of GDMT to target doses should be considered. In addition, consideration should be given to substituting an angiotensin receptor neprilysin inhibitor for an ACE inhibitor or ARB.

Q. Is implantable-cardioverter defibrillator (ICD) generator change indicated in HFrecEF patients?

It is unclear if the subset of HFrecEF patients who had an ICD placed for primary prevention of SCD when the LVEF was ≤ 35%, continue to benefit from ICD therapy once the LVEF has improved. A recent meta-analysis supports the notion that there is persistent arrhythmic risk among HFrecEF patients, with a 3.3% per year rate of appropriate ICD therapy among those with LVEF ≥ 45%.10 An analysis of SCD HeFT (Sudden Cardiac Death in Heart Failure Trial) also showed that patients who had an improvement in EF to >35% during follow-up accrued a similar mortality benefit with an ICD as those whose EF remained at ≤35%.11 Even though there are no prospective trials of ICD therapy among HFrecEF populations, available data support ICD generator change for most patients with HFrecEF.12 ICD replacement is all the more indicated, if a deleterious genetic mutation associated with high arrhythmia risk is present (eg: LMNA, SCN5A, and FLNC etc), or if history of appropriate shocks is documented.13

CRT should of course be maintained in HFrecEF patients, because electrical dyssynchrony and forward LV remodelling are known to recur with loss of resynchronization.14

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What's new in Heart Failure? - American College of Cardiology's Annual Scientific Session, 2021.

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1. The LIFE trial

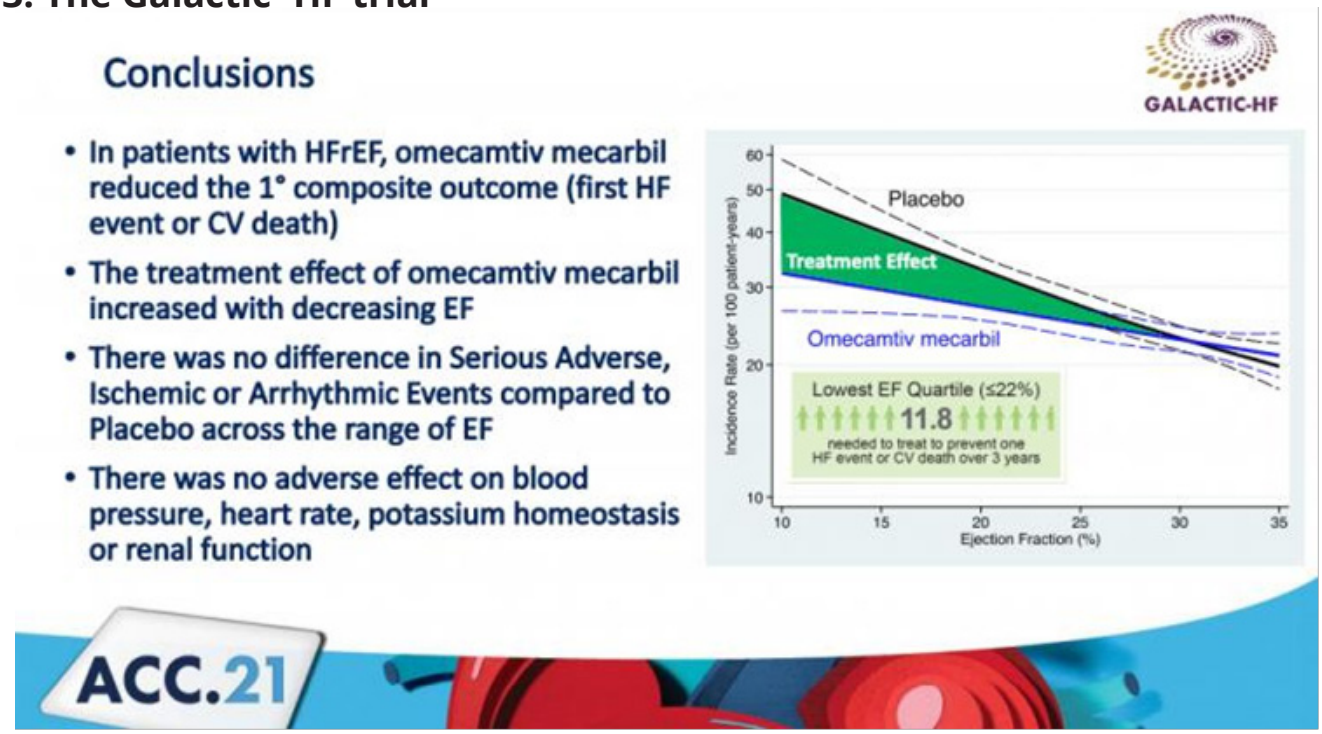
- The goal of the trial was to assess the efficacy and safety of sacubitril/valsartan compared with valsartan in patients with advanced heart failure with reduced ejection fraction (HFrEF).
- Eligible patients were randomized in a 1:1 fashion to either sacubitril/valsartan (starting dose 24/26 mg or 49/51 mg BID, up-titrated to 97/103 mg BID if tolerated after 4 weeks) (n = 167), or valsartan (starting dose 40 or 80 mg BID, up-titrated to 160 mg BID if tolerated) (n = 168). Total number enrolled: 335. Duration of follow-up: 24 weeks. Mean patient age: 60 years. Percentage female: 27%.
- Inclusion criteria: NYHA class IV symptomatology in previous 3 months. Receiving guideline-directed medical therapy (GDMT) for HF for ≥3 months and/or intolerant to GDMT. Left ventricular EF (LVEF) ≤35%. B-type natriuretic peptide (BNP) ≥250 pg/ml or N-terminal pro-BNP (NT-proBNP) ≥800 pg/ml. Systolic blood pressure ≥90 mm Hg. ≥1 additional objective finding of advanced HF. Current inotropic therapy/use of inotropes within 6 months. ≥1 HF hospitalization within 6 months. LVEF ≤25% within 12 months. Decreased peak VO2 within 12 months. 6-minute walk test distance <300 meters within 3 months.
- The results of this trial indicate that the combination sacubitril/valsartan did not reduce NT-proBNP or clinical outcomes among patients with advanced HFrEF and comorbidities.
- Ref: Presented by Dr. Douglas L. Mann at the American College of Cardiology Virtual Annual Scientific Session (ACC 2021), May 17, 2021 and published online at JACC Heart Failure. 2020 Oct;8(10):789-799. doi: 10.1016/j.jchf.2020.05.005. Epub 2020 Jun 10.

2. The PIROUETTE trial

- The trial was done to evaluate pirfenidone, an antifibrotic agent, compared with placebo among patients with heart failure with preserved ejection fraction (HFpEF).
- Patients with HFpEF were randomized to pirfenidone (n = 47) versus placebo (n = 47). Total number of enrollees: 94. Duration of follow-up: 12 months. Mean patient age: 78 years. Percentage female: 47%. Percentage with diabetes: 34%.
- Inclusion criteria: HFpEF (left ventricular EF [LVEF] ≥45%). N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥300 pg/ml. Extracellular volume ≥27%, as assessed by cardiac magnetic resonance imaging (MRI).

- The primary outcome, change in myocardial extracelluar volume (%) from baseline to 52 weeks, was -0.7 in the pirfenidone group compared with 0.5 in the placebo group (p = 0.009).
- Secondary outcomes: No difference in diastolic function. No difference in 6-minute walk distance. No difference in Kansas City Cardiomyopathy Questionnaire summary score.
- Conclusion: Among patients with HFpEF, pirfenidone appeared to be beneficial. This medication was associated with a modest reduction in myocardial fibrosis, as assessed by cardiac MRI, compared with placebo. The clinical significance of this finding is unknown.
- Ref: Presented by Dr. Christopher Miller at the American College of Cardiology Virtual Annual Scientific Session (ACC 2021), May 17, 2021. Not yet published in peer reviewed journal

3. The Galactic -HF trial



- Omecamtiv mecarbil, a selective cardiac myosin activator works by improving the ability for heart muscle cells to contract and operates through a different biological pathway than any of the current heart failure medications.
- The research is an extended analysis of data from GALACTIC-HF, a trial involving more than 8,200 participants that found omecamtiv mecarbil significantly improved outcomes in terms of a composite of cardiovascular death or heart failure events among patients with heart failure with reduced ejection fraction.
- The trial investigated omecamtiv mecarbil in patients with heart failure with an ejection fraction of less than or equal to 35%.
- The original trial had met its primary endpoint, which was a composite of time to first heart failure event or death due to cardiovascular causes, and the benefit was predominantly driven by reductions in heart failure events, with no significant improvement in the rate of death from cardiovascular causes compared to placebo. An additional benefit, omecamtiv mecarbil did not adversely

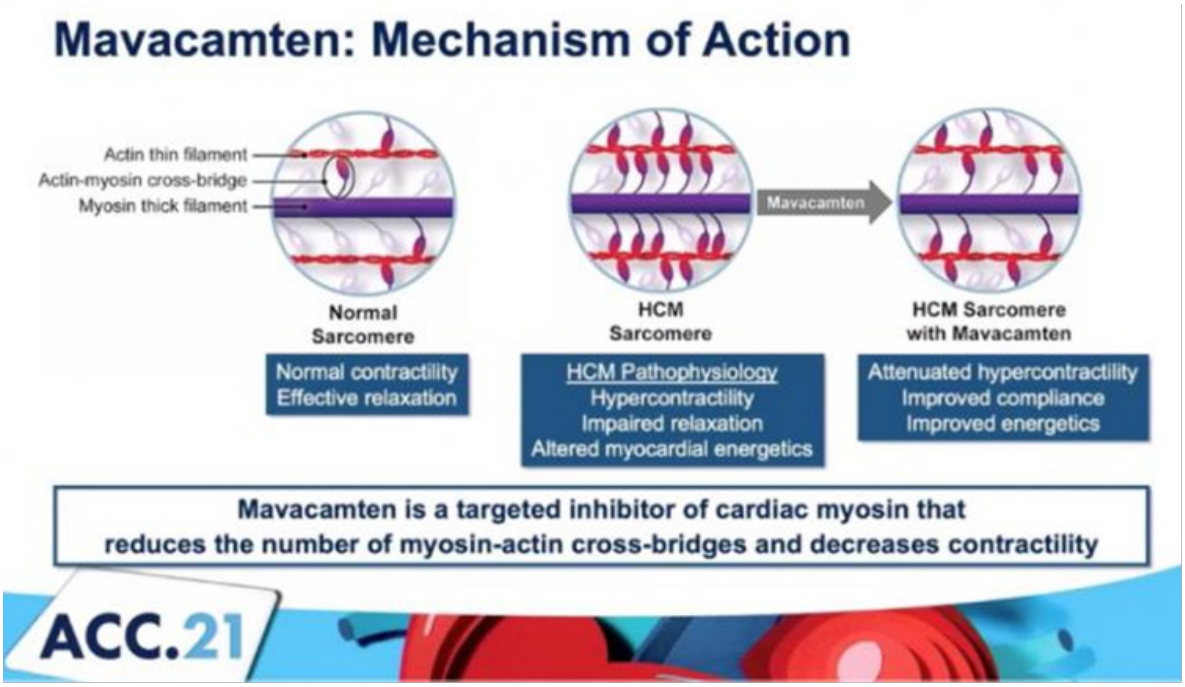
affect blood pressure, heart rate, potassium concentrations or renal function, even when used alongside current heart failure medications. In addition, there was no increase in cardiac ischemic or ventricular arrhythmic events.

- In the new analysis, researchers found that the relative and absolute benefits from omecamtiv mecarbil significantly improved with progressively lower ejection fraction. Patients in the two lowest quartiles in terms of ejection fraction had a 15-17% reduction in the risk of dying from cardiovascular causes or being hospitalized with heart failure, compared to 8% for the entire patient population. In the lowest quartile, the absolute risk reduction was 7.4 per 100 patient years, meaning that treating fewer than 12 patients with omecamtiv mecarbil would result in preventing one cardiovascular death or heart failure hospitalization.
- The study did not show a clear benefit of omecamtiv mecarbil among patients with ejection fraction higher than about 30%.
- Ref: Teerlink JR, Diaz R, Felker M, et al., on behalf of the GALACTIC-HF Investigators. Effect of Ejection Fraction on Clinical Outcomes in Patients Treated With Omecamtiv Mecarbil in GALACTIC-HF. J Am Coll Cardiol 2021;May 17:[Epub ahead of print].

4. The PARADISE -MI trial

- The study is the first large trial to examine whether sacubitril/valsartan can reduce heart failure and associated hospitalizations and deaths in patients post-heart attack who face a high risk of developing heart failure.
- The PARADISE-MI trial enrolled 5,661 patients in 41 countries who had survived a heart attack less than a week before enrolling in the study. None of the patients had heart failure, but all were considered to face a high risk of developing it. Eligible patients were randomized in a 1:1 fashion to either sacubitril/valsartan (target dose 97/103 mg BID) (n = 2,830) or ramipril (target 5 mg BID) (n = 2,831). Duration of follow-up: 23 months. Mean patient age: 64 years. Percentage female: 24%.
- Inclusion criteria: Presentation with AMI. Left ventricular ejection fraction (LVEF) ≤40% with or without pulmonary congestion. Plus one of the following: age ≥70 years, atrial fibrillation, estimated glomerular filtration rate (eGFR) <60, diabetes mellitus, prior MI, LVEF <30%, Killip class ≥III, ST-segment elevation MI (STEMI) without reperfusion.
- Principal Findings: The primary outcome of cardiovascular (CV) death, first HF hospitalization, or outpatient HF for sacubitril/valsartan vs. ramipril, was: 11.9% vs. 13.2% (p = 0.17). CV death: 5.9% vs. 6.7% (p = 0.20). HF hospitalization: 6% vs. 6.9% (p = 0.17)
- Interpretation: The results of this trial indicate that the combination sacubitril/valsartan did not reduce the primary endpoint in a contemporary enriched AMI population, compared with ramipril.
- Ref: Jering KS, Claggett B, Pfeffer MA, et al. Prospective ARNI vs. ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction (PARADISEMI): design and baseline characteristics. Eur J Heart Fail 2021;Apr 12:[Epub ahead of print].

5. The EXPLORER-HCM Trial



- Mavacamten is a potential first-in-class, oral, allosteric modulator of cardiac myosin, under investigation for the treatment of conditions in which excessive cardiac contractility and impaired diastolic filling of the heart are the underlying cause. Mavacamten reduces cardiac muscle contractility by inhibiting excessive myosin-actin cross-bridge formation that results in hypercontractility, left ventricular hypertrophy and reduced compliance.
- The goal of the trial was to evaluate mavacamten, a cardiac myosin inhibitor, compared with placebo among patients with hypertrophic obstructive cardiomyopathy.
- Eligible patients were randomized to mavacamten 5 mg daily (n = 123) versus placebo (n = 128) for 30 weeks. Duration of follow-up: 30 weeks. Mean patient age: 59 years. Percentage female: 46%.
- Inclusion criteria: ≥18 years of age. Hypertrophic obstructive cardiomyopathy (left ventricular outflow tract [LVOT] gradient ≥50 mm Hg).LV ejection fraction (LVEF) 55%. New York Heart Association (NYHA) class II-III symptoms
- Principal Findings: The primary outcome, ≥1.5 ml/kg/min increase in pVO2 with ≥1 NYHA class improvement or ≥3.0 ml/kg/min increase in pVO2 with no worsening of NYHA class at 30 weeks, occurred in 37% of the mavacamten group compared with 17% of the placebo group (p = 0.0005).
- Secondary outcomes: Post-exercise LVOT gradient change from baseline to week 30: -47 mm Hg in the mavacamten group vs. -10 mm Hg in the placebo group (p < 0.0001). pVO2 change from baseline to week 30: 1.4 ml/kg/min in the mavacamten group vs. -0.1 ml/kg/min in the placebo group (p = 0.0006)

- Kansas City Cardiomyopathy Questionnaire (KCCQ): At 30 weeks, change in KCCQ-overall summary score: 14.9 for mavacamten vs. 5.4 for placebo (difference +9.1, $p < 0.0001$)
- Interpretation: Among patients with hypertrophic obstructive cardiomyopathy, mavacamten was superior to placebo. This medicine improved functional capacity and health status, as assessed by KCCQ. Mavacamten was well tolerated. Mavacamten was associated with a significant reduction in post-exercise LVOT gradient compared with placebo.
- Ref: Spertus JA, Fine JT, Elliott P, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet 2021;397:2467-75.

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Covid Vaccine Induced Myocarditis

Introduction:

Since the outset of the pandemic of COVID-19 , varied presentation of the disease have been reported. Cardiovascular manifestations of COVID-19 are receiving attention due to a spectrum of disease manifestation namely myocardial infarction, myocarditis, heart failure, arrhythmia and cardiogenic shock. Of them, myocarditis has been one of the leading causes of death due to COVID -19. As the pandemic progressed, various measures were taken to mitigate the disease spread. Among them ,the most effective are the vaccines against the virus. However, like the virus itself, viral particles used in the vaccine are being linked to side effects which at times can lead to serious health issues including myocarditis ; specially the m-RNA vaccines . Considering the imminent approval of m-RNA vaccines in India and consequently the expected wide spread public administration, this topic assumes a lot of significance.

Pathophysiology of myocarditis in Covid19 :

SARS-CoV-2 virus enters cell by attaching its surface spike protein to the cell membrane protein angiotensin converting enzyme 2 (ACE2) found on ciliated columnar epithelial cells of the respiratory tract, type II pneumocytes, as well as myocardial cells. After gaining entry, intracellular SARS-CoV-2 virus interferes with the stress granule formation via its accessory protein and continues to replicate inside the cell and causes damage to it. It has been hypothesized that the viral myocarditis seen in case of Covid19 is a combination of direct cell injury and T-lymphocyte–mediated cytotoxicity, which can be amplified by the cytokine storm. Interleukin 6 (IL-6) plays the central role as a mediator of cytokine storm and activates T lymphocyte to cause further release of inflammatory cytokines and ultimately stimulating more T lymphocytes, leading to a vicious cycle of activation of immune system and subsequent myocardial damage.

Myocarditis in COVID vaccination candidates:

There are a few instances where Covid19 vaccination has triggered myocarditis in the recipients. On 23rd June 2021 the US Centre for Disease Control and Prevention (CDC) had given a warning signal about the likely association between mRNA vaccine and myocarditis and pericarditis. The Vaccine Adverse Events Reporting System had found 1226 cases of myocarditis and pericarditis out of 300 million doses of Pfizer and Moderna vaccines. US FDA, CDC and American College of Physician and American Medical Association opined in a joint statement that mentioned side effect was extremely rare and mild. Exact reason mechanism behind this side effect is still unknown.

Demography of the cases :

It has been found that, mostly the adolescent males and young adults had developed this side effect after taking mRNA vaccine mostly after the second dose. According to CDC data, after 3625574 second doses, administered to men aged between 18-24 years, 233 cases of myocarditis or pericarditis have been reported. Whereas after 5237262 second doses in the women of same age group, 27 cases were reported. Both the reported cases were higher than expected numbers, signifying clear safety concern in young males and to a lesser extent to females.

First reporting of side effect:

A small number of this side effect was first reported by Israel's health ministry at the end April 2021. Total 275 cases of myocarditis were found in Israel between December 2020 and May 2021 among five million people who were vaccinated. Cases were found concentrated in the males with age group 16-19 years usually after the second dose. In UK, till 16th June 53 cases of myocarditis and 33 cases of pericarditis were reported after mRNA vaccine but the numbers were below or within the expected background range of general population. In the USA , the military also reported a total of 23 cases of myocarditis and pericarditis out of 2.8 million doses of mRNA vaccine administered. All of them were male with age ranges between 20-51 years.

Severity of myocarditis:

The reported cases of myocarditis and pericarditis were usually mild, benign and self-limiting and usually treated with NSAIDS. There are no long term data currently available regarding the consequences of mild vaccine related myocarditis.

Whether it is an association or causation:

As the reported side effect is occurring relatively in the younger age group and a large number of young population has already been vaccinated, at present it is difficult to determine whether its relationship with the vaccination is causation or association.

Possible mechanisms:

The possible mechanism of myocardial injury may be the direct infection by the vaccine-virus components, an immune-mediated response, or a combination of both direct and indirect effects. The mRNA vaccines can potentially generate a very high antibody response (delayed type hypersensitivity) in young people, thus producing a response similar to multisystem inflammatory syndrome in children (MIS-C). The mRNA vaccines can also induce a non-specific innate inflammatory response or a molecular mimicry mechanism between the viral spike protein and an unknown cardiac protein. Vaccine

induced induction of anti-idiotype cross-reactive antibody-mediated cytokine expression in the myocardium can cause inflammation of myocardium and pericardium. The other probable mechanism includes the RNA in the vaccine itself, a potent immunogen, can affect by cytokine activation of pre-existing auto reactive immune cells as young people usually have higher seroprevalence of SARS-CoV-2 even if they are asymptomatic during the COVID- 19 pandemic.

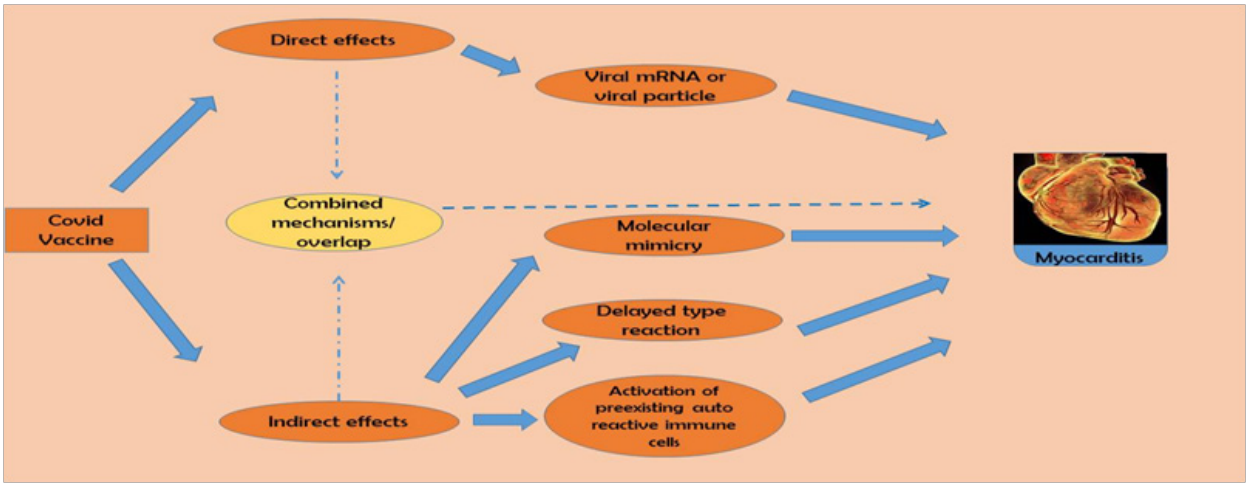

Figure 1: Possible mechanisms of vaccine induced myocarditis.

Conclusion:

Although, there were cases reported on vaccine induced myocarditis found in the 16-28 years age group mostly after the second dose, approximately 95 percent of the reported myocarditis cases were only mild. This side effect is considered an important one but quite uncommon, arising in about 12.6 cases per million second doses administered. Substantial morbidity and mortality associated with COVID-19 infection, including risk of cardiac injury in the form of myocarditis are already recognized and strong evidence of effectiveness of vaccination in prevention of COVID 19 infection has been documented. Based on these findings, the Centre for Disease Control and Prevention (CDC) opined that the benefits of being vaccinated against SARS-CoV-2 virus far outweigh the very small risk of getting myocarditis related to the vaccine itself and recommended to continue the mRNA vaccination but with a warning of possible side effects related to myocarditis. Although there are concerns regarding rare adverse event such as myocarditis following immunization, it should not diminish overall confidence in the importance of vaccination.

Suggested Reading:

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Multisystem Inflammatory Syndrome in Children (MIS-C) and Heart Failure

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What is MIS-C?

Multisystem Inflammatory Syndrome in Children (MIS-C) is a term coined by the Centers for Disease Control and Prevention and overlaps with the pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) defined by the UK Royal College of Pediatrics and Child Health. This condition has similarities to viral myocarditis, Kawasaki disease (KD), Kawasaki shock syndrome, and toxic shock syndrome and is associated with heart failure. While data suggests that children below 18 years are relatively less susceptible to SARS-CoV-2 (40% vs 80%) and are less often symptomatic (20-30% vs 60%), MIS-C has emerged as a major cause of pediatric heart failure[1]. MIS-C may be considered a post-infectious immunological complication following exposure to SAR-CoV-2, rather than an acute infection.

Pathophysiology of heart failure in MIS-C

The pathophysiology of MIS-C is thought to be due to a hyperimmune response to the SARS-CoV-2 in a genetically susceptible child. MIS-C is characterized by continued activation of the adaptive immune response driven by persistent antigen presence. Younger children have a relatively less robust host response to SARS-CoV-2. They experience a very mild underdiagnosed acute infection period in which host immune activation is not able to clear the system from the virus completely; thus, a persistent antigen stimulation exists. This causes a cytokine storm, as represented by the elevated biomarkers, leading to cardiomyocyte injury. Heart failure in MIS-C can also be due to microvascular dysfunction, viral invasion of cardiomyocytes resulting in cellular damage and ischemic injury[2].

Clinical presentation of MIS-C

The diagnostic criteria for MIS-C and related syndromes are presented in table 1. The mean age of presentation is 8 years with no gender predilection[3]. Epidemiologically, most cases of MIS-C were reported 4 – 5 weeks following the peak incidence of covid-19 in the concerned region. Many children with MIS-C have no history of a symptomatic respiratory infection and test negative for SARS-CoV-2 by polymerase chain reaction, but have developed SARS-CoV2–specific IgG antibodies, suggesting the initial infection occurred at least 2 weeks before the development of MIS-C.

Fever is the most common symptom upon presentation, followed by abdominal pain/ diarrhea, rash, and conjunctival injection. Laboratory abnormalities in MIS-C include elevated C-reactive protein (99%), lactate dehydrogenase (99%), procalcitonin (96%), B-type natriuretic peptide and N-terminal pro-BNP (95%), cardiac troponins (93%), D-dimers

(90%), serum interleukin-6 (88%) and serum ferritin (79%)[4]. The biomarker levels tend to peak early, most often at admission itself with only minimal increase during hospitalization. Neutrophilia and lymphopenia are the common hematological abnormalities.

MIS-C and ventricular dysfunction

Acute onset left ventricular (LV) dysfunction is the most common cardiac manifestation of MIS-C (50 – 70% of cases)[5]. Elevated cardiac troponins (64-95%) and brain natriuretic peptides (73-95%) are also associated with presentation in shock and LV dysfunction. Severe LV dysfunction has been reported in up to 30% of cases of MIS-C, and cardiogenic shock in 40%. However, most studies have noted recovery of ventricular function in the majority with supportive treatment with/ without extracorporeal membrane oxygenation support (median of 2 days from diagnosis of LV dysfunction to recovery)[6]. The rare patient can become inotrope dependent with need for ventricular assist device or heart transplantation.

Cardiac MRI in MIS-C

Cardiac MRI in the acute phase of MIS-C often reveals elevated T1 mapping values and T2-STIR ratio suggesting myocardial hyperemia and edema[5]. T1 values are often normal when MRI is done beyond two weeks of the disease course, with resolution of interstitial edema related changes and normal T2 values. Late gadolinium enhancement is usually negative in MIS-C.

MIS-C and the coronaries

Coronary artery dilatation and aneurysm formation is one of the dreaded complications of MIS-C (8 – 24% of cases). While the exact pathophysiology of the same is still under investigation, vasculitis triggered by circulating inflammatory mediators and vessel wall disruption is the postulated mechanism, quite like coronary artery lesions (CAL) in KD. Giant coronary artery aneurysms (z score ≥10) are reported in MIS-C but rare. Older age of presentation (9-11 years), lower absolute lymphocyte and platelet counts, higher ferritin and D-dimer levels, and higher likelihood of having elevated troponin or BNP in MIS-C differentiate it from classical KD[7]. MIS-C tends to be more sinister with >50% incidence of LV dysfunction and shock as opposed to 5 – 10% in KD[8].

MIS-C and cardiac arrhythmias

Electrocardiographic abnormalities have been reported in up to a third of hospital admissions with MIS-C, which return to normal in 72% of cases[4]. They include ST-T changes and PR interval prolongation. First degree AV block has been reported in 6 – 16% of admissions for MIS-C, and more often in teenagers[9]. However, progression to advanced degrees of atrioventricular block is unusual. This could be related to the administration of immunosuppressive measures in these patients. QTc prolongation is variably seen in these children and is influenced by the drugs used in treatment. Ventricular arrhythmias have been described in MIS-C, though infrequent. There are rare instances of refractory ventricular arrhythmias in MIS-C needing ECMO support.

Studies have shown that ventricular repolarization is impaired even in asymptomatic children with covid-19 infection. QT dispersion (QTd), QTc dispersion (QTcd), Tp-e, Tp-e dispersion, Tp-e/QT ratio, and Tp-e/QTc ratio have been noted to be prolonged in children with acute covid-19 infection[10]. Ventricular tachycardia and fibrillation are more common in acute covid-19 rather than MIS-C.

Management of MIS-C and heart failure

Early administration of intravenous immunoglobulin (IVIg) 2g/kg over 24-48 hours (max 100g) has been reported be associated with early recovery of LV function and is considered the first line of management for acute heart failure in MIS-C. The treatment protocol is inspired from the management guidelines for KD. As in KD, treatment response is indicated by defervescence and resolution of associated symptoms. Aspirin 3 – 5 mg/kg/day is given concomitantly for its antiplatelet action. Almost all patients with MIS-C and heart failure require inotropic support.

Intravenous methylprednisolone (10 – 30 mg/kg/day, max 1g/day) are useful in high-risk cases with failure to respond to IVIg. The Ministry of Health and Family Welfare and the Indian Academy of Pediatrics recommend concomitant administration of intravenous methylprednisolone with IVIg for life-threatening MIS-C with cardiogenic shock[11]. The threshold for use of corticosteroids is MIS-C should be low, considering its role in downregulating inflammatory cascades, platelet adherence and activities of T and B lymphocytes. If symptoms persist for 48 – 72 hours of treatment, or there is clinical worsening, IVIg may be repeated with consideration for antibiologicals.

The interleukin-1 antagonist, Anakinra (2 – 10 mg/kg/dose 6 – 12 hourly) and anti-interleukin 6 receptor monoclonal antibody, Tocilizumab (4 – 8 mg/kg/dose) are options for persistent severe inflammatory states. The TNFα blocker, Infliximab is another useful agent in management of MIS-C. The role of antiviral therapy in MIS-C is uncertain.

All patients with MIS-C should be closely monitored for coronary artery dilatation. Low molecular weight Heparin (Enoxaparin) is recommended for giant aneurysms (z score >10) or presence of thrombus in the coronaries. Patients with severe LV dysfunction also benefit with Enoxaparin during hospitalization for MIS-C.

Prognosis:

While heart failure in MIS-C is life-threatening, it responds well to aggressive therapy. Ventricular dysfunction improves in the majority in the first week of treatment. Arrhythmias have also tended to improve. Patients with persistent ventricular dysfunction or coronary artery dilatation will require long term Aspirin and/or anticoagulation. Follow up evaluation should involve ECG, echocardiography and BNP/NT-proBNP recording. Holter monitoring may be done if there are any conduction delays or ectopy on follow up. The suggestions of a continuous antigenic stimulus, inability to clear the viral infection, in younger pediatric patients developing MIS-C may raise the question of whether children are truly the silent spreaders of SARS-CoV2.

Table 1: Case definitions of the Multisystem Inflammatory Syndrome in Children (MIS-C) by the Center of Disease Control (CDC) and the World Health Organization (WHO).

CDC Case Definition (Age < 21 years)	WHO Case Definition (Age 0-19 years)	Royal College of Pediatric and Children health
All the 4 findings below:	**All the 4 findings below:**	**All the 4 findings below:**
1. Fever ≥ 38 or subjective for ≥ 24 hours	1. Fever for ≥3 days	1. Fever
2. Laboratory inflammation (C-reactive protein, erythrocyte sedimentation rate, fibrinogen, D-Dimer, ferritin, LDH, IL6, neutrophilia and hypoalbuminemia)	2. Elevated inflammatory markers (eg. erythrocyte sedimentation rate, C-reactive protein, or procalcitonin)	2.Inflammation (neutrophilia, elevated CRP and lymphopenia)
3. Severe illness requires hospitalization	3. No other obvious microbial cause of inflammation	3. Evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder)
4. ≥ 2 organ systems involved (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic and neurologic)	4. Multisystem involvement (rash, bilateral non-purulent conjunctivitis, mucocutaneous inflammation, hypotension or shock, cardiac dysfunction, [pericarditis, valvulitis and coronary abnormalities (seen by echocardiogram or elevated BNP)], coagulopathy (elevated PT, PTT, D-Dimer) and acute GI symptoms (diarrhea, vomiting and abdominal pain)	4. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
No other plausible diagnosis	SARS-CoV-2 infection by PCR, serology or antigen or exposure to an individual with COVID-19	SARS-CoV-2 PCR testing may be positive or negative
SARS-CoV-2 infection or exposure defined as		

1. Positive PCR, serology or antigen test		
2. COVID-19 exposure within four weeks prior to onset		
Additional KD full or partial criteria should still be considered as MIS-C and in any death with evidence of SARS-CoV-2, MIS-C should be considered.		

BNP: Brain natriuretic peptide, COVID-19: Corona Virus Disease-19, GI: gastrointestinal, IL6: interleukin 6, KD: Kawasaki disease, LDH: lactate dehydrogenase, PT: prothrombin time, PTT: partial thromboplastic time, SARS-CoV2: severe acute respiratory syndrome coronavirus 2.

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Universal Definition and Classification of Heart Failure 2021

From "Heart Failure Cardiologists" to "Heart Function cardiologists"

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In March 2021, three major Heart Failure(HF) Societies - the Heart Failure Society of America (HFSA), the Heart Failure Association of the European Society of Cardiology (HFA-ESC) and the Japanese Heart Failure Society (JHFS) released a Universal Definition and Classification of Heart Failure, which standardizes language and practices around the definition and classification of heart failure (HF). The document has also been endorsed by four other National HF Societies including our HFAI.

Why new Definition?

The Cardiology community is aware that there is a lack of standardization of definition of HF across scientific societies and this leads to under-diagnosis of HF and is found as a hindrance to the intake of guideline directed therapy which saves lives. For example the academic definitions such as the "heart's inability to meet the metabolic demands", were not applicable or measurable in most patients with early stages of HF. The new Universal Definition and Classification of Heart Failure "provides a definition that is clinically relevant and simple but conceptually comprehensive" as per the writing committee.

HEART FAILURE ASSOCIATION OF INDIA

The Universal Definition of HF is Endorsed by Heart Failure Association of India

What are the changes in the new Definition?

A. Heart Failure:

The new definition necessitates more objective criteria which adds substantial sensitivity and specificity to the diagnosis which can lead to more accurate identification, and fewer misdiagnoses.

HF is a clinical syndrome with current or prior

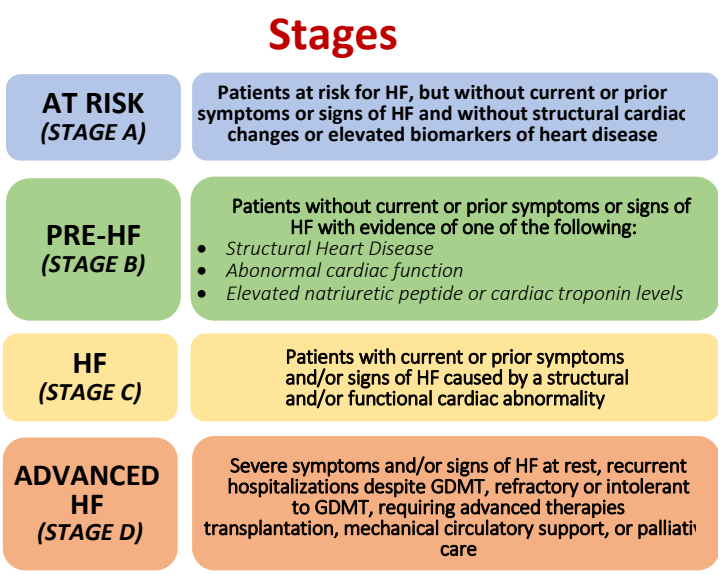
- Symptoms and or signs caused by a structural and/or functional cardiac

And corroborated by at least one of the following:

- Elevated natriuretic peptide levels
- Objective evidence of cardiogenic pulmonary or systemic congestion

B. Stages of HF

Traditionally, the AHA classification categorized HF into 4 stages : A, B, C or D. But this classification was not clear to patients as for example in cancer staging.



Stage A HF - "At risk for HF" – Eg: Hypertensives, Diabetics etc.

Stage B HF - Pre-HF – Here biomarkers have been brought in to give more clarity of definition. Also with this definition it becomes easy for the physician to convey to the patient why we need to initiate specific treatment strategies that are critically important to prevent HF in the pre-HF. ie, progressing from Stage B to Stage C.

Stage C – Clinical, symptomatic HF

Stage D – Advanced HF

C. Revised classification of HF based on Ejection Fraction

The new Universal Definition also has made two notable changes in classification of HF based on EF.

1. One is the change in the name of HF mid-range EF to HF with mildly reduced (EF 41-49%)
2. The other more notable change is the new subcategory "HF with improved EF" (HFimpEF). Initially these patients were classified as HF with "Recovered EF". We know that those with HF patients with improved ejection fraction even to almost normal levels may still be at risk of decompensation once GDMT is discontinued. So the term "recovered EF" may give a false sense of security to both patients and care givers.

Classification By EF

HF with reduced EF (HFrEF)

- HF with LVEF < 40%

HF with mildly reduced EF (HFmrEF)

- HF with LVEF 41-49%

HF with preserved EF (HFpEF)

- HF with LVEF > 50%

HF with improved EF (HFimpEF)

- HF with a baseline LVEF of < 40%, a 10-point increase from baseline LVEF, and a second measurement of LVEF of > 40%

D. The new language of Heart Failure. – Revised clinical trajectory Terminologies.

The revised clinical trajectory terminologies highlight two facts

1. Even when the patient is clinically stable there are many avenues to optimize therapy which can improve outcomes, prevent further worsening and/or deterioration or development of adverse outcomes. So “Stable HF” is replaced with “Persistent HF”.
2. As mentioned above, Improvement in clinical status, biomarkers and EF usually does not mean the HF is cured. Most of the time, there is some residual disease and it re-surfaces once disease modifying therapies are withdrawn like Beta blockers and RAAS blockers as we saw n TRED-HF trial. So it is essential that these drugs are continued under supervision. So the preferred term is “HF in remission” than “recovered HF”.

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Heart Failure Quiz

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In this edition we have a heart failure quiz dedicated to famous people in Cardiology particularly related to heart failure .Many are pioneers in this field who have paved the way for cardiology to move forward , embrace newer technologies and reach current stature. Identify the person in each scenario.Happy quizzing!

1. Considered as the father of Cardiac Electrophysiology ,he coined the term clinical science.This was one of his famous quotes "The very essence of cardiovascular practice is the early detection of heart failure".

2. "A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory filling pressure" was his definition of Heart failure. Born in India, In 1950 he wrote in the preface of his landmark book ". . . yet there is already plenty of evidence to show that we are in danger of losing our clinical heritage and of pinning too much faith in figures thrown up by machines."

3. English Physician best known for the use of foxglove plant to treat dropsy in 1785. He gained renown for his botanical writings and in recognition for his study of the properties of barium carbonate, this mineral was subsequently named after him.

4. Awarded Nobel Prize Medicine in 1988 he developed the drug cimetidine in 1970 and another pivotal class of drugs used in heart failure . In 1946 he found that "the way patients were treated was unacceptably insensitive", decided against a career as a medical practitioner and instead took up a career in physiology .

5. "A pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues" Born in Vienna in 1929 he was the founding chairman for the TIMI study group .***"The best book of cardiology is the patient itself."*** was one of his favourite quotes .

6. "Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients".a study published in American Journal of Cardiology in 1967 was the basis of this classification for risk stratifying Mortality in Acute Myocardial Infarction patients.

7. In 1970 developed a technique for bedside hemodynamic monitoring ,the concept for the invention is said to have been derived from watching the wind playing with sails in Santa Monica, California.

8. The Surgeons words "For a dying man it is not a difficult decision because he knows he is at the end. If a lion chases you to the bank of a river filled with crocodiles, you will leap into the water, convinced you have a chance to swim to the other side." The dying man here is Louis Washkansky in 1967.Who is the Surgeon ?

9. Brought in the concept of hemodynamic subsets in the therapy of Acute Myocardial Infarction patients and he lead a team that developed Coronary angioscopy.

10. The first successful implantation of an artificial Heart was implanted by surgeon Denton Cooley (1920-2016) on April 4, 1969, at St. Luke's Episcopal Hospital in Houston.Who developed this ?

How Many did you get Right?

Turn the page and see...

HF QUIZ ANSWERS

1.Sir Thomas Lewis

2.Paul Hamilton Wood

3. William Withering

4. Sir James Whyte Black

5.Eugene Braunwald

6. Thomas Killip III & John T.Kimball

7. William Ganz and H.J.C Swan

8. Christiaan Neethling Barnard

9. James .S.Forrester III

10. Domingo Santo Liotta

We would love to hear from you !

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

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NOTES

* This is a creative expression that refers to mechanistic changes that were observed with Sacubitril Valsartan in HFrEF patients. Treatement with Sacubitril Valsartan significantly reduced least square geometric mean ratios of NT-ProBNP with associated improvements in indices fo cardiac remodelling such as LVEDVI, LVESVI, LVEF and E/e'.

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*IHD – Ischemic Heart Disease, HF – Heart Failure All claims are based on authentic data, available on request. #Data on file

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HF: Heart Failure; CHF: Congestive Heart Failure; CKD: Chronic Kidney Disease

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