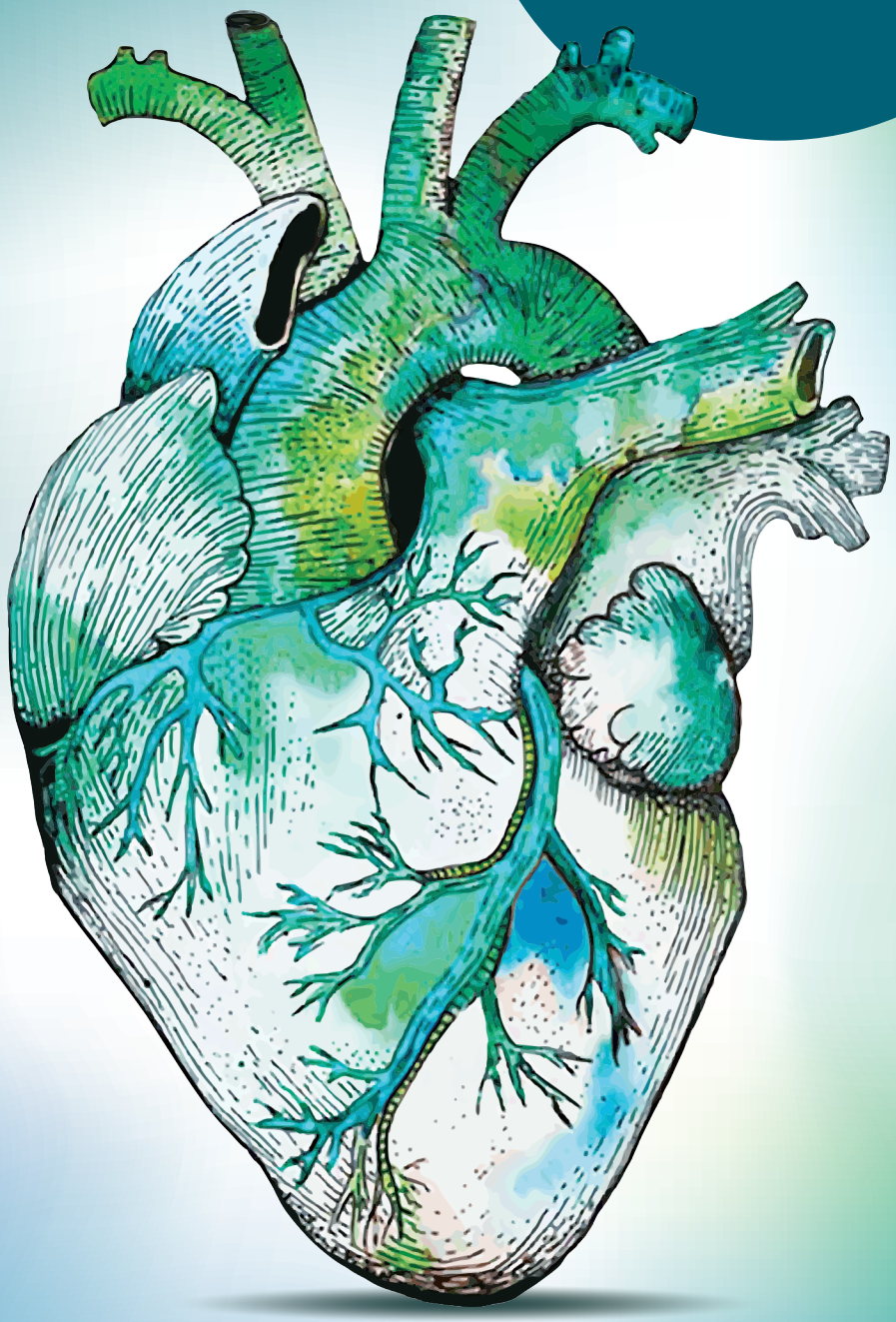
A Journal of
Cardiological Society of India
Kerala Chapter

p-ISSN: 2347-5267
e-ISSN: 2454-6755

May - October 2020 Volume - 9, Issue 1

www.keralaheartjournal.in

KHJ
KERALA HEART JOURNAL



Editor: Dr. Stigi Joseph

KERALA HEART JOURNAL
(p-ISSN: 2347-5267), (e-ISSN: 2454-6755)
January – June 2020, Volume – 8, Issue – 1.

Editorial Board

Editorial Secretariat:
Stigi Joseph
Little Flower Hospital and
Research Centre,
Angamaly, Kochi. 683572.
Mob: +91 9446279889
Email: editorkhj@gmail.com

Editorial Secretariat
Stigi Joseph

CSI Kerala Office Bearers

KERALA HEART JOURNAL
(p-ISSN: 2347-5267), (e-ISSN: 2454-6755)
January – June 2020, Volume – 8, Issue – 1.

Table of Contents

Dr. Damodhar Reddy Gouni, MD*
Dr. Navin Mathew MD.DM
Dr. Hisham Ahmed MD DM, Rajiv C, MD DM.
Department of Cardiology
Amrita Institute of medical sciences
Correspondence: * damodher.s@gmail.com

Original Article:

LIGHT CHAIN CARDIAC AMYLOIDOSIS AND RESPONSE TO "CYBOR-D"

A SINGLE TERTIARY CARE CENTER EXPERIENCE

Running Head: Treatment Response and profile of Amyloidosis

ABSTRACT: The survival of untreated patients with Light chain (AL)cardiac amyloidosis(CA) is poor. We wanted to see response trends of Cyclophosphamide + Bortezomib +Dexamethasone (CYBOR D) according to new revised Mayo staging, functional NYHA class, Left ventricular ejection fraction(EF%) and diastolic dysfunction(E/e'), Global longitudinal strain(GLS) and mortality at 1 year follow up. We collected data of 137 marrow or tissue biopsy-proven patients with AL amyloidosis from 2012 to 2017 retrospectively from our hospital database. Of which 84 had CA.64 patients on CYBOR D regimen were included finally after excluding 20 cases. The mean age was 62 +/- 10 years with 68% males. The number of patients in improved, No change and worsened category according to MAYO staging was 37 (58%), 23(36%),4 (6%), NYHA class was 39(60.9%), 11(17.1%) and 14(22%). EF % were 11(17.1%), 39(60.9), 14(22%).E/e' were 21(32.8%),27(42.1%) & 16 (25%) respectively. NT pro-BNP improved in 39 (60.9%). Out of 52 cases with GLS data available 23(44.2%) shown improvement, no change in 26 (50%) 2 and worsened in 3 (5.8 %).16 patients (25%) died at the end of 1 year follow up. Mortality rates in improved , no change and worsened groups of GLS were 0(0%) ,13(50%) & 3(100 %), EF % group were 0(0%),2(5.1%),14(100%),E/e' group were 0(0%),2(7.4%),14(87.5%), Mayo staging group were 1(2.3%),11(68.8%),4(100%)respectively .In conclusion, worsening mayo staging, GLS, EF%, Diastolic dysfunction, has high mortality rates. No change group in GLS has a better correlation than EF% and DD of predicting mortality next to mayo staging.

KEYWORDS: Cardiac amyloidosis, CYBOR D Treatment response, Mayo staging, Global longitudinal strain, Ejection fraction, Diastolic dysfunction.

ABBREVIATIONS:

AL	:	Light chain amyloidosis, CA: Cardiac Amyloidosis
CyBor D	:	Cyclophosphamide, Bortezomib, Dexamethasone
NYHA	:	New York Heart Association, GLS: Global Longitudinal Strain
DD:		Diastolic dysfunction, LV EF: Left Ventricular Ejection Fraction
NT Pro BNP	:	N Terminal pro Brain Natriuretic peptide
cTNT	:	Cardiac Troponin T, dFLC: Difference of Free Light Chains
CAD	:	Coronary Artery Disease

Introduction: Light chain(AL)amyloidosis is a systemic disease of protein misfolding with the 3 monoclonal light chain component of intact immunoglobulin being the precursor protein leading to amyloid deposits within tissues. Progressive deposition leads to organ dysfunction and eventually organ failure. Cardiac dysfunction is observed in up to 60% of patients with AL amyloidosis and portends a poor prognosis.1. Median survival is <1 year versus ~8 years in patients without cardiac involvement.2 The original Mayo Clinic cardiac staging system developed by Dispenzieri et al. was instrumental in establishing a means of rapidly identifying this high-risk group of patients.3The currently preferred staging system is revised Mayo Staging System that utilizes the aforementioned biomarkers Troponin T (cTNT)> 0.025 ng/ml, NT-pro BNP(>1800 pg/ml) and dFLC (Difference of involved free light chain (FLC)and uninvolved free light chain (FLC)> 18 mg/dl)to stratify disease severity4. A score of 1 was assigned for each of the above variables. The patients were categorized into stages 1 through 4 based on scores of 0, 1, 2, and 3, respectively.

It is now the standard prognostic model used in the stratification of AL amyloid. Experience with bortezomib-containing regimens holds promise with high rates of deep clonal responses achieved.5-12 In this study, we present a single tertiary care center experience of cyclophosphamide, bortezomib, and dexamethasone (CyBor D) used as upfront therapy in patients who were prognosticated according to New Revised Mayo Clinic staging. We examine treatment response trends in functional NYHA class, NT pro-BNP, Revised mayo staging, Left ventricular systolic and diastolic function, Global longitudinal strain and the impact on overall survival at 1 year follow up.

METHODOLOGY:

About 137 marrow or tissue biopsy proved patients with AL amyloidosis from 2012 to 2017 were identified retrospectively from our Amrita institute of medical sciences hospital database. Of which 84 had Cardiac involvement. 20 cases were excluded (11 patients had underlying CAD and 9 patients lost to follow up). Finally, 64 patients with cardiac light chain amyloidosis on the CYBOR D regimen were included in the study. It includes induction therapy with Cyclophosphamide (300 mg/m2 IV or oral weekly), Bortezomib (2mg) weekly SC OR IV, Dexamethasone (IV 40 mg weekly) for 16 weeks followed by maintenance therapy with Bortezomib/Thalidomide/Lenalidomide.13Cardiac involvement was defined by the presence of low voltage on 12-lead electrocardiography (all limb leads <0.5 mV) with echocardiographic evidence of a mean LV wall thickness of more than 12 mm in the absence of hypertension or other potential causes of LV hypertrophy or by evidence of amyloid deposits on endomyocardial biopsy14(available in 10% of patients). Inclusion criteria were :

1) Pre chemotherapy baseline echo and a post-chemo echo at 6 months and 1 year follow up.

2) Free light chain, NT Pro BNP, Troponin T levels at baseline and end of 1 year follow up.

Echocardiographic studies were performed using a GE ECHO vivid E9 machine and viewed on the offline ECHOPACS software workstation (GE Medical Systems). Standard measurements of ventricular dimension, diastolic parameters, and ejection fraction were made according to the guidelines of the American Society of Echocardiography.15Longitudinal strain was calculated by manually correction after automatic software tracing of the length of the ventricular midwall in the apical 2-chamber, 3-chamber, and 4-chamber views and taking the average of these three measurements. Normal average GLS cutoff taken as > -17%.16

Treatment response trends were categorized into three groups

1) Improved, 2) No change, 3) Worsened.

The cardiac response is considered if decrease in NT-pro BNP by >30% and 300 pg/mL (if baseline NT-pro-BNP >650 pg/mL) or >2-point decrease in NYHA class (if baseline NYHA class III or IV).17 We considered one stage improvement or worsening in Mayo staging as improved/worsened group. Echocardiographically improvement in GLS and EF is considered if > 10% improvement from baseline.18 1 point improvement/worsening in diastolic dysfunction grade(Average E/e' <8 :Grade 1, 8-12 : grade 2,> 12 :Grade 3) is considered an improved or worsened group.Comparisons of continuous variables between baseline and follow-up were performed using the Mcnemar Bowker test. Comparison of GLS, EF, Diastolic function, Mayo staging versus mortality done by Pearson's chi-square test. A P value of <0.001 was considered significant. All analyses were performed using SPSS 21 software.

RESULTS :

Totally 64 patients were on CYBOR-D regimen included in the study. The mean age was 62 +/- 10 years with 68% males. The number of patients with improvement in NYHA functional class 39(60.9%), no change in 11(17.1%) and worsened in 14(22%)(P <0.001). NT pro-BNP improved in 39 (60.9%) and no change in 25(39%)(P<0.001).

At baseline number of patients (n=4)in stage 1 mayo ,(n= 37)in stage 2,(n=17) in stage 3,(n=6) in stage 4(Table 1).Improvement in new revised mayo staging seen in n=37 (58%), no change n=23(36%), worsened n=4 (6%)(P <0.001)(Table 1).Left ventricular ejection fraction at baseline (n=10) with normal EF(55-60%),(n=37) with mild LV systolic dysfunction (EF 45-55%),(n=10) with moderate LV systolic dysfunction (EF 35-45%),(n=7) with Severe LV systolic dysfunction

Table 1 . Clinical, Biomarker and Echo Variables at baseline and post chemotherapy follow up of *AL cardiac amyloidosis

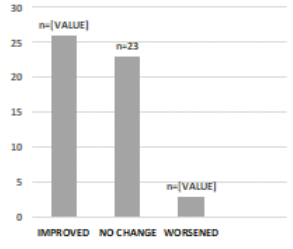
VARIABLES	BASELINE (Percentages %)	POST CHEMO (Percentages %)	P VALUE
NYHA FUNCTIONAL CLASS (n=64)			<0.001
1	11(17%)	25(39%)	
2	34(53%)	28(44%)	
3	16(25%)	9(14%)	
4	3(5%)	2(3%)	
NT PRO BNP *(n=64)			-
>30% REDUCTION	-	39	
<30% REDUCTION	-	25	
DIASTOLIC DYSFUNCTION (n=64)			<0.001
NORMAL	0 (0%)	1(1.6%)	
1	23(36%)	27(42.1%)	
2	28(43.7%)	23(36%)	
3	13(20.3%)	13(20.3%)	

VARIABLES	BASELINE (Percentages %)	POST CHEMO (Percentages %)	P VALUE
LV EF % *(n=64)			<0.001
>55%	10(15.6%)	6(9.3%)	
45-55%	37(57.8%)	38(59.5%)	
35-45%	10(15.6%)	14(21.9%)	
<35%	7(11%)	6(9.3%)	
AVG GLS % *(n=52)			<0.001
>-17 %	1(2%)	13(25%)	
-12 %TO -17%	29(55.7%)	25(48%)	
<12%	22(42.3%)	14(27%)	
REVISED MAYO STAGE (n=64)			<0.001
1	4(6.2%)	37(57.8%)	
2	37(58%)	15(23.4%)	
3	17(26.5%)	4(6.3%)	
4	6(9.3%)	8(12.5%)	

*AL –Amyloid light chain ,NT PRO BNP - N Terminal Pro Brain Natriuretic peptide , LVEF – Left ventricular ejection fraction , AVG GLS – Average Global Longitudinal Strain

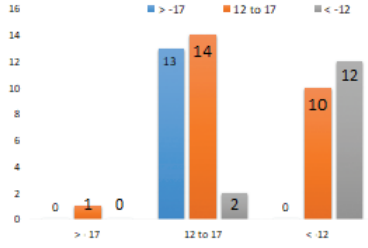
Figure 1

*GLS response trends on post chemotherapy follow up(n=52) represented as change in GLS



x-axis showing improved,no change,worsened groups of GLS
And y -axis showing the variable numbers (n)
* GLS = Global Longitudinal strain

*GLS response trends baseline & post chemotherapy follow up(n=52) Represented as three subgroups according to severity of GLS impairment



x-axis showing three sub groups of GLS (<-12 to >-17) at basline(n)
And y -axis showing GLS response post chemo followup (n) in three subgroups
* GLS = Global Longitudinal strain

and improvement in EF seen in 11(17.1%), no change in 39(60.9),worsened in 14(22%)(P<0.001)(Table1).Diastolic dysfunction(E/e')at baseline were (n=23) grade 1(E/e' <8) ,(n=28) in grade 2(E/e' 8 to 12),(n=13) in grade 3(E/e' >12) (Table 1).and improvement in E/e' seen in n=21(32.8%), no change in n=27(42.1%) & worsened in n=16 (25%)(P <0.001) Out of 52 cases with GLS data available ,baseline GLS (n=1) with >-17 %, (n=29) with -12 to -17 ,(n=22) with <-12(Table 1).Of which n=23(44.2%) shown improvement, no change in n=26 (50%) and worsened in n=3 (5.8 %)(P<0.001).

Out of 64 patients , n=48 (75%) patients survived and n=16 patients (25%) died at the end of 1 year follow up(P <0.001). Mortality rates in improved , no change and worsened groups of GLS were n=0(0%),n=13(50%) &n=3(100%), EF% group were n=0(0%),n=2(5.1%),n=14(100%), E/e' group were n=0(0%),n=2(7.4%),n=14(87.5%), Mayo staging group were n=1(2.3%),n=11(68.8%),n=4(100%)(P<0.001)respectively.

\We noted 100% mortality in worsened groups of GLS,EF% and Mayo staging and 87.5 % mortality in worsened E/e' group.

All patients in the improved group showed 0 % mortality except for 1 patient (2.3%) mortality in mayo staging due to severe sepsis. All patients in the worsening category of Mayo staging, GLS, EF, DD showed significant mortality. So improved and worsened groups have a good correlation between mayo staging, GLS, EF, E/e'. But no change in EF and E/e' group showed no significant mortality compared to no change in the Mayo staging and GLS group which showed

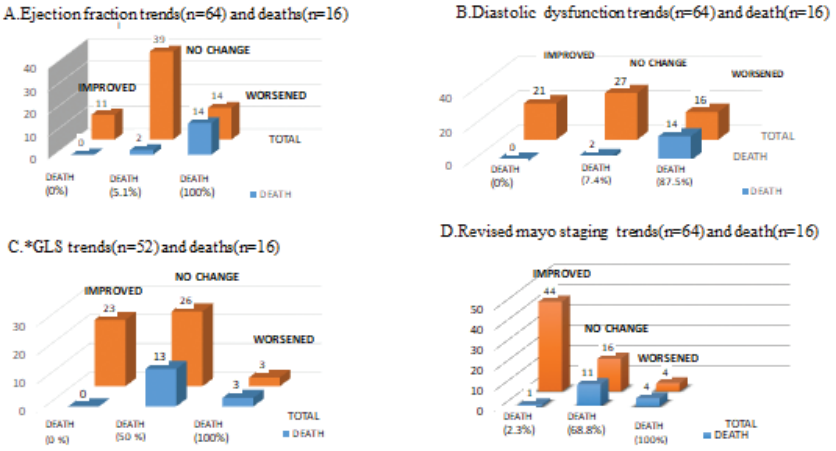
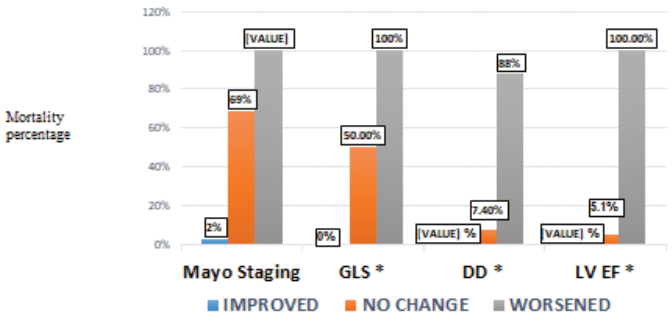


Figure 2. Comparison of echocardiographic parameters and Mayo staging categorised into improved,no change,worsened groups(Orange bars) post chemotherapy and number of deaths(Blue bars) and Percentges. Frequencies shown on y- axis .*GLS = Global longitudinal strain

Figure 3. Mortality percentage comparison of improved , No change ,Worsened groups of Mayo staging, GLS ,DD and LVEF on post chemotherapy follow up.



*GLS – Average Global Longitudinal Strain, DD –Diastolic dysfunction, LVEF – Left ventricular ejection fraction
Blue, orange, grey colors of bars on x -axis indicating improved, No change, worsened groups and y axis showing mortality percentages

68.8 % and 50 % mortality respectively. This signifies that no change in GLS with cut off <-17 % after chemotherapy suggests poor prognosis next to Mayo staging and can be used as an additional prognostic value to mayo staging in predicting mortality.

Discussion:

The most critical prognostic marker concerning survival from Light chain amyloidosis diagnosis is the extent of cardiac involvement. This study demonstrates the prognostic value of GLS for risk stratification among patients with AL amyloidosis undergoing chemotherapy. Not only is GLS strongly prognostic, these data indicate that GLS supplements the well-validated cardiac biomarker staging for survival among patients treated with chemotherapy.

This study confirms existing published data demonstrating the superiority of GLS as a predictor of survival compared with LVEF and diastolic dysfunction in patients with cardiac amyloidosis.19-22 It is well recognized that GLS, a measure of longitudinal LV function, is more sensitive and accurate than LVEF in the assessment of myocardial contractility, particularly in cardiomyopathy conditions.23,24. Longitudinal LV mechanics, which are governed primarily by the subendocardial layer, are the most sensitive and vulnerable to myocardial disease. This likely explains why GLS remains a strong prognostic predictor despite normal LVEF. Other investigators have also shown the incremental value of GLS for the assessment of outcome compared with clinical, echocardiographic, and serum biomarkers in patients with AL amyloidosis.25-27 The variability in GLS cut off values for the discrimination of survivors from non-survivors that has been reported in the literature is likely attributable to differences in the study population, duration of follow-up, treatment regimens, and platforms used for GLS estimation.

Cardiac biomarkers are important predictors of outcome in amyloidosis, serving as the basis for the now widely accepted revised Mayo Clinic cardiac staging system. Median overall survival in months from stage I to IV are 94%,40%,14%,5.8% respectively and 5 year survival rates are 59 %,42%,20%,14% respectively . It has been proposed that a rapid response is integral to overcoming the early deaths seen in this disease and improve outcomes in patients with advanced cardiac involvement. This principle guided the development of CyBor D as an ideal regimen for use in the upfront setting. The addition of bortezomib to the traditional alkylator and steroid backbone further improves response rates. Cyclophosphamide has the advantage of being easier to dose in patients with renal insufficiency. The present study examines the use of CyBor D in a single-center setting. Outcomes in AL amyloidosis are proving to be more favorable than previously expected, especially in patients who live long enough to benefit maximally from therapy. In conclusion, our results show that initiation of the CYBOR D regimen in all stages gives significant survival benefit at the end of 1 year. Worsening mayo staging, GLS, EF%, Diastolic Dysfunction has high mortality rates. And on the same lines in significant mortality with improvement in Mayo staging, GLS, EF, and Diastolic Dysfunction. No change(intermediate) group in GLS with cut-off <-17 % has a better correlation than EF% and Diastolic Dysfunction of predicting mortality next to Mayo staging. The limitations of this study are small sample size and single-center design.

References

1. Shah KB, Inoue Y, Mehra MR. Amyloidosis and the heart: a comprehensive review. Arch Intern Med 2006;166:1805–1813.
2. Gertz MA. Immunoglobulin light chain amyloidosis: 2011 update on diagnosis, risk stratification, and management. Am J Hematol. 2011;86(2):180-6.
3. Dispenzieri A1, Gertz MA, Kyle RA, Lacy MQ, Burritt MF, Therneau TM. Serum cardiac troponin and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol. 2004;22(18):3751-7.
4. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, Laumann K, Zeldenrust SR, Leung N, Dingli D, Greipp PR, Lust JA, Russell SJ, Kyle RA, Rajkumar SV, Gertz MA. The revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol. 2012;30(9):989–95.
5. Davies FE, Wu P, Jenner M, Srikanth M, Saso R, Morgan GJ. The combination of cyclophosphamide, Velcade, and dexamethasone induce high response rates with comparable toxicity to Velcade alone and Velcade plus dexamethasone. Haematologica. 2007;92(8):1149-50.

6. Wechalekar AD, Lachmann HJ, Offer M, Hawkins PN, Gillmore JD. Efficacy of bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease. Haematologica. 2008;93(2):295-8.

7. Reece DE, Sanchorawala V, Hegenbart U, Merlini G, Palladini G, Fermand JP, et al. Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of phase 1 dose-escalation study. Blood. 2009;114(8):1489-97.

8. Kastritis E, Wechalekar AD, Dimopoulos MA, Merlini G, Hawkins PN, Perfetti V, et al. Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis. J Clin Oncol. 2010;28(6): 1031-7.

9. Zonder J, Sanchorawala V, Snyder R, Matous J, Terebelo H, Janakirama N, et al. Rapid haematologic and organ responses in patients with AL amyloid treated with bortezomib plus melphalan and dexamethasone. Amyloid Journal of Protein Folding Disorders. 2010;17(s1):86-7.

10. Reece DE, Hegenbart U, Sanchorawala V, Merlini G, Palladini G, Bladé J, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study. Blood. 2011;118(4): 865-73.

11. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, Bello N, Spong J, Reeder CB, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces a rapid and complete hematologic response in patients with AL amyloidosis. Blood. 2012;119(19): 4391-4.

12. Venner CP, Lane T, Foard D, Rannigan L, Gibbs SD, Pinney JH, et al.Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood. 2012;119(19):4387-90.

13. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, Bello N, Spong J, Reeder CB, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces a rapid and complete hematologic response in patients with AL amyloidosis. Blood. 2012 May;119(19):4391–4.

14. Gertz MA, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PN, Merlini G, Moreau P, Ronco P, Sanchorawala V, Sezar O, Solomon A, Grateau G. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18–22 April 2004. Am J Hematol 2005;79:319–328.

15. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39e14.

16. Kobayashi Y, Ariyama M, Kobayashi Y, Giraldeau G, Fleischman D, Kozelj M, Vrtovec B, Ashley E, Kuznetsova T, Schnittger I, Liang D, Haddad F. Comparison of left ventricular manual versus automates derived longitudinal strain: implications for clinical practice and research. Int J Cardiovasc Imaging 2016;32:429–437.

17. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol. 2012; 30(36):4541-4549.

18. Dubrey SW, Cha K, Skinner M, LaValley M, Falk RH. Familial and primary (AL) cardiac amyloidosis: echocardiographically similar diseases with distinctly different clinical outcomes. Heart 1997;78:74–82.

19. Bellavia D, Pellikka PA, Abraham TP, Al-Zahrani GB, Dispenzieri A, Oh JK, et al. Evidence of impaired left ventricular systolic function by Doppler myocardial imaging in patients with systemic amyloidosis and no evidence of cardiac involvement by standard two-dimensional and Doppler echocardiography. Am J Cardiol 2008;101:1039-45.

20. Ternacle J, Bodez D, Guellich A, Audureau E, Rappeneau S, Lim P, et al. Causes and consequences of longitudinal LV dysfunction assessed by 2D strain echocardiography in cardiac amyloidosis. JACC Cardiovasc Imaging 2016;9:126-38.

21. Buss SJ, Emami M, Mereles D, Korosoglou G, Kristen AV, Voss A, et al. Longitudinal left ventricular function for prediction of survival in systemic light-chain amyloidosis: incremental value compared with clinical and biochemical markers. J Am Coll Cardiol 2012;60:1067-76.

22. Koyama J, Falk RH. Prognostic significance of strain Doppler imaging in light-chain amyloidosis. JACC Cardiovasc Imaging 2010;3:333-42.

23. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol 2014;63(25 Pt A):2751-68.

24. Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J 2016;37: 1196-207.

25. Buss SJ, Emami M, Mereles D, Korosoglou G, Kristen AV, Voss A, et al. Longitudinal left ventricular function for prediction of survival in systemic light-chain amyloidosis: incremental value compared with clinical and biochemical markers. J Am Coll Cardiol 2012;60:1067-76.

26. Salinaro F, Meier-Ewert HK, Miller EJ, Pandey S, Sanchorawala V, Berk JL, et al. Longitudinal systolic strain, cardiac function improvement, and survival following treatment of light-chain (AL) cardiac amyloidosis. Eur Heart J Cardiovasc Imaging 2016;18:1057-64.

27. Boynton SJ, Geske JB, Dispenzieri A, Syed IS, Hanson TJ, Grogan M, et al. LGE provides incremental prognostic information over serum biomarkers in AL cardiac amyloidosis. JACC Cardiovasc Imaging 2016;9

Dr. Benoy Sebastian. MD. DM.
Consultant Gastroenterologist,
Medical Trust Hospital,Ernakulam.
Correspondence: benoygastro@gmail.com

Review Article:

PROTON PUMP INHIBITORS IN DAY-TO-DAY PRACTICE

Introduction

Proton pump inhibitor therapy has revolutionized the management of gastroesophageal reflux disease (GERD), peptic ulcers, functional dyspepsia, and H.pylori infection. PPI use continues to increase globally and concern about its misuse is growing. More than 50% of PPIs are prescribed inappropriately.1,2. Well established side effects of PPIs such as headache, diarrhea and constipation are minor and are easily managed. Recent publications, however describing numerous putative, at times serious side effects have raised an alarm among patients and practitioners alike.

Some of the putative adverse effects of PPIs are related to their profound suppression of gastric acid secretion. With such acid suppression, micro-organisms that would have been destroyed by gastric acid might colonize the upper gastrointestinal tract, altering its microbiome.3 The ingested microbes, that otherwise would have been killed by gastric acid might survive and cause infections. Gastric acid inhibition can influence the uptake of certain vitamins and minerals and the absorption of certain drugs like warfarin, ketoconazole, etc.

Elevation of serum gastrin levels is another potentially undesirable effect of gastric acid suppression by PPIs.Gastrin released by G cells in the pyloric gland mucosa of the antrum stimulates acid secretion by parietal cells in the gastric body and fundus. Gastrin is a growth factor that can increase proliferation in Entero Chromaffin Like (ECL) cells, in Barrett metaplasia and in the colon.4,5

Cardiovascular Complications

PPIs are prodrugs and are primarily metabolized by the cytochrome P450 isoenzyme CYP2C19. Because the an-

ti-platelet drug clopidogrel is activated by CYP2C19, there has been concern that PPIs may decrease clopidogrel's antiplatelet effect. The inhibitory effect is maximum with omeprazole followed by lansoprazole and esomeprazole. However, pantoprazole and rabeprazole are weak inhibitors with minimum interaction with clopidogrel.6 The COGENT study, a randomized controlled trial published in 2010, provided reassurance that PPIs do not meaningfully interact with clopidogrel.7 COGENT randomized patients who were receiving daily aspirin to a combination pill containing omeprazole and clopidogrel versus placebo. When results from 3761 patients were analyzed, there was no difference in the cardiovascular event rate between omeprazole-clopidogrel (4.9%) compared to clopidogrel alone (5.7%). These results make it highly unlikely that there is a large increase in risk for myocardial infarction (MI) due to PPIs in patients taking clopidogrel. Later a systematic review of published data, which included 10 laboratory studies involving healthy volunteers and 33 clinical studies concluded that an adverse effect of PPI use on clinical outcomes in patients taking clopidogrel cannot be substantiated.8 A European Expert Position paper summarises that the potential negative clinical impacts of some PPIs on the therapeutic efficacy of clopidogrel are still controversial. Given the pharmacokinetic data and inconclusive clinical evidence, PPIs with weaker inhibition of CYP2C19 are preferred in combination with clopidogrel compared with those with stronger inhibition such as omeprazole.9 The same paper recommends safe administration of any PPI with prasugrel, ticagrelor and aspirin whenever indicated.9

Subsequently, it was postulated that PPIs might increase the risk for MI based on a different mechanism, ie, that they may directly blockade vascular nitric oxide synthase to enhance vascular contractivity.10However the clinical evidence linking PPIs to an increased risk of major adverse cardiac events has been weak. A 2017 meta-analysis of 17 GERD trials reported a hazard ratio of only 1.7 for patients taking PPIs.11The quality of evidence, however, was moderate or low, cardiovascular outcomes were not study endpoints and confounding variables such as obesity, smoking, alcohol and family history were not assessed. Three studies were subsequently published, in 2018, that support the cardiovascular safety of PPIs. A Danish registry study of 214 998 individuals, without prior history of MI or stroke who underwent an elective upper endoscopy between 1997 and 2012, reported only a minimal increase in ischaemic stroke and MI for current PPI users (hazard ratio, 1.13 and 1.31, respectively).12Although obesity, smoking and exercise status were addressed, a major limitation of this and all such observational studies is the inability to correct for unmeasured confounding variables and medication adherence.

PPI and anticoagulants

PPIs have been shown to reduce warfarin metabolism and clearance leading to prolongation of INR. They share the same CYP enzyme for hepatic metabolism (mainly CYP2C19)13. Omeprazole is reported to have greater potential to alter CYP activity than the newer PPIs.14So while co prescribing warfarin with PPI more vigilant INR monitoring is required.PPI has no major impact on the pharmacokinetic profile of newer anticoagulants like dabigatran, rivaroxaban, and apixaban9

Renal Injury

PPIs can produce acute interstitial nephritis, which is an idiosyncratic hypersensitivity reaction and may recur on re-exposure.15,16 It is also shown that PPIs can lead to chronic kidney disease (CKD) and the worsening of CKD. In a large study, Xie et al compared 173,321 PPI users with 20,270 H2RA users. The baseline e GFR was normal in both groups. They were followed up to 5 years for incident CKD, defined as e GFR less than 60ml/min/1.73m2.They found 1.8% absolute annual excess for risk for CKD. The exact mechanism of renal injury is not known.17

Malabsorption of Vitamins and minerals.
Hypomagnesemia

PPIs can cause hypomagnesemia due to reduced intestinal absorption.18 A meta-analysis of nine observational studies that included a total of 109,798 patients found that those who took a PPI had a significantly higher risk (RR 1.43, 95% CI, 1.08-1.88) of developing hypomagnesemia as compared with those who did not.19 Discontinuation of PPI results in normalization of the serum levels. This potential risk has led to recommendations to monitor serum magnesium levels in specific patients at high risk for hypomagnesemia.

Hypocalcemia and Fracture Risk

Hypocholhydria induced by PPI can theoretically decrease calcium absorption. But the risk is limited mainly to the carbonate form (water-insoluble) and may be overcome by ingestion of a slightly acidic meal.20 A link between PPIs and increased fracture risk is based on several potential mechanisms including hypochlorhydria-associated malabsorption of calcium or vitamin B12, gastrin-induced parathyroid hyperplasia, and osteoclastic vacuolar proton pump inhibition. Numerous studies have examined this association and many but not all have reported a positive association.21 These observational data were limited by unmeasured and/or residual confounding factors. The results regarding the presence of a dose- or duration-based response have also been inconsistent, as have studies that investigated the effect of PPI therapy on bone mineral density (BMD) based on dual-energy X-ray absorptiometry (DXA).22Currently, there are no data to support the routine use of bone mineral density monitoring among PPI users

Anemia due to Malabsorption of Iron and Vitamin B12

Dietary iron is in the ferric form (Fe3+) and is not soluble in pH >3. This is converted to ferrous form (Fe2+) for absorption in the acidic pH. Cobalamin is a water-soluble vitamin highly bound to dietary protein. In normal gastric acidity states, hydrochloric acid and pepsin act to release cobalamin, allowing it to bind to salivary R proteins transferring cobalamin to intrinsic factor. The cobalamin–intrinsic factor complex then allows the absorption of cobalamin in the terminal ileum. Hypochlorhydria induced by PPIs is purported to interfere with this absorption process, leading to anemia.

However, in most cases, decreased absorption does not appear to be of clinical significance. One exception may be in patients who require oral iron supplementation. Such patients may need a higher dose or longer duration of supplementation.23 But the absorption of oral B12 supplements is not affected by PPIs

Dementia and Cognitive Decline

Build up of amyloid-b (Ab) protein predisposes to Alzheimer's disease. Microglial cells use V-type ATPases to degrade amyloid-b, and PPIs may block V-ATPases to increase isoforms of amyloid-b in mice.24 Building on this, two recent clinical studies tested for an association between exposure to PPIs and dementia. Haenisch et al followed 3,327 adults aged 75 years or more with serial neuropsychiatric examinations. PPIs were associated with a 38% increased risk for dementia.25 Gomm et al extended these results by retrospectively querying an insurance database covering more than half of the German population over 75 years old 26. They found a 44% higher risk for dementia in regular users of PPIs compared to non-users. It is well established that patients who initiate PPIs have more comorbidities than those who do not, and this may be particularly true for older adults. In this study, adults selected for PPIs had strikingly higher baseline rates of depression, stroke, and polypharmacy. Although the study adjusted for these baseline characteristics, additional uncaptured baseline differences between PPI users and non-users may explain the differences in rates of dementia rather than exposure to PPIs.

Increased Risk of Infections Enteric Infections

Gastric acid plays a crucial role in killing the ingested microorganisms and there are reports suggesting acid suppression with PPI can increase the risk of infections with enteric organisms such as Salmonella and Campylobacter.27Observational studies suggest an approximately 50% relative risk of Clostridium difficile infection; pseudo membraneous colitis (PMC) with PPI usage.28However the risk is modest compared to antibiotics induced PMC. Certain studies suggest higher risk in specific populations like children.29

Alterations in gut bacteria due to hypochlorhydria may lead to changes in intestinal permeability and translocation of bacteria across the gut wall. Studies show a 2-fold relative risk for spontaneous bacterial peritonitis (SBP) associated with exposure to PPIs in cirrhotics.30 However, accurate ascertainment of PPI exposure has unique challenges in cirrhotics who are frequently hospitalized and consequently likely to be exposed to PPIs intermittently. There are various other confounding factors like gastrointestinal bleeding which can lead to SBP in a cirrhotic.

Pneumonia

In observational studies, PPIs have been associated with increased risk for community-acquired pneumonia.31 However, this risk was seen mainly in those who started PPIs recently than those using long-term PPIs.32,33 This suggests

either that PPIs are markers for uncaptured acute events (eg, hospitalizations) or that they are being prescribed for early symptoms of undiagnosed pneumonia or may a co-prescription with antibiotics. The OBERON study randomized 2426 ambulatory adults to a PPI versus placebo for 26 weeks for ulcer prevention and found similar rates of pneumonia (0.9% with PPIs vs 1.9% with placebo).34In a post hoc, manufacturer-sponsored analysis of 24 short-term RCTs, the incidence of pneumonia was similar in patients randomized to PPIs compared to placebo.35 Randomized studies of PPIs for stress ulcer prophylaxis in the ICU have not shown an association between PPIs and ventilator-associated pneumonia.36

Problems with the studies identifying PPI associated complications

The putative risks of PPIs, described previously, were identified primarily as weak associations found in observational studies, and there are contradictory reports regarding the validity of each of those putative risks. Observational studies are notoriously unreliable for identifying important cause and effect relationships. In general, unless relative risks in cohort studies exceed 2 to 3, or odds ratios in case-control studies exceed 3 or 4, associations in observational research findings should not be considered credible." Most of the putative PPI risks, discussed previously, were identified in studies with relative risks and odds ratios considerably below those limits.

Unfortunately, even strong associations found in observational studies cannot establish cause and effect because of the substantial biases that often confound those studies. For example, some observational studies have identified a strong association (odds ratios >4) between PPI usage and the development of esophageal adenocarcinoma.37 One possible conclusion for this observation is that PPIs are a risk factor for esophageal cancer. GERD, however, is a well-established, strong risk factor for esophageal adenocarcinoma, and PPIs are commonly prescribed to treat GERD. Consequently, it seems more likely that the indication for the PPI prescription (ie, GERD) is the important cancer risk factor, not the PPIs used to treat GERD. This is an example of confounding by indication, a bias that often is difficult to exclude in observational studies on putative PPI side effects.

Recently a study by Moayyedi et al38 evaluated potential causality for several reported proton pump inhibitor associations with one of the weightiest forms of causal evidence: experimental data. They included more than 17,000 patients from 33 countries who were randomized to pantoprazole versus placebo, followed for a median of approximately 3 years, and evaluated prospectively for potential complications (COMPASS study). The study found an increased risk of enteric infections among pantoprazole users, a result found in both the intention-to-treat and "as-treated" analyses, which excluded people who stopped their medications. This association makes sense as gastric acid, normally decreases bacterial load in food, so hypochlorhydria may increase the risk of enteric bacterial infections. The authors found no increased risk for several of the most feared associations previously reported, such as cardiovascular disease, kidney disease, dementia, bone fracture, pneumonia, etc.

Summary

Though the evidence is weak, it is prudent not to dismiss the data entirely. The weak association does not strongly support causality, but it does not exclude it either. Even a small increase in the risk of a catastrophic event like myocardial infarction or stroke is important and, unfortunately, the uncertainty about PPI risks is unlikely to be resolved easily.

The best way to avoid drug side effects is to not prescribe a drug unless there is a clear indication and then to use it in the recommended dosage. As discussed previously, however, PPIs often are used inappropriately and often are prescribed in higher-than-recommended dosages. PPIs are now available as OTC in many countries, patients can have free access to them and tend to take these drugs for long periods without seeking any medical attention.39

The use of PPIs continues to grow every year and this calls into the question of their overuse and misuse. It has been calculated that more than 50% of PPIs are prescribed inappropriately in internal medicine wards and in general practice.40 The common situations include over-prescription in patients with functional dyspepsia, unnecessary co-prescription with antibiotics, co-prescription with NSAIDs, steroids, antiplatelets and anticoagulants without valid indication, overuse in ICUs and post-operative wards and use in cirrhotics fearing bleeding risk.41

Before prescribing a PPI, the physician should carefully consider whether there is a valid indication and, if there is, to

confirm the appropriate dosing for the condition. For patients already taking PPIs, the physician should carefully review the medical record and determine whether the continuation of PPI therapy is appropriate. Despite a large number of studies, the overall quality of evidence for PPI adverse effects is low. When PPIs are appropriately prescribed, their benefits are likely to outweigh their risks. When PPIs are inappropriately prescribed, modest risks become important because there is no potential benefit. Education is the key to guide hospital doctors and general practitioners to the correct use of PPIs, according to worldwide published guidelines

References

1. van Vilet EP et al, Inappropriate Prescription of proton pump inhibitors in two pulmonary medicine wards.European J Gastroenterol and Hepatol 2008;20;608-612
2. Reid M, Keniston A et al, Inappropriate prescription of proton pump inhibitors in hospitalized patients.J Hosp Med.2012;7;421-425
3. Naito Y, Kashiwagi K, Takagi T, et al. Intestinal dysbiosis secondary to proton- pump inhibitor use. Digestion 2018;97:195–204.
4. Dockray GJ, Varro A, Dimaline R, et al. The gastrins: their production and biological activities. Annu Rev Physiol 2001;63:119–39.
5. Haigh CR, Attwood SE, Thompson DG, et al. Gastrin induces proliferation in Barrett's metaplasia through activation of the CCK2 receptor. Gastroenterology 2003; 124:615–25.
6. Michael AS et al, Clopidogrel Proton Pump Inhibitors, and Risk of Adverse Clinical outcomes among PCI treated ACS patients. Adverse clinical outcomes among PCI treated ACS patients. A meta analysis.J Mang Care Spec Pharm.2016:22 (8): 939-40
7. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010;363:1909–1917
8. Focks JJ, Brower MA et al, Concomitant use of clopidogrel and PPI.Impact on platelet function and clinical outcome.A systematic review.Heart.2013;99(8):520
9. Stefan Agewall, M Cutaneo et al, Expert position paper on the use of proton pump inhibitors in patients with cardiovascular diseases and antithrombotic therapy.Europ Heart J.2013;34,1708-1715
10. Ghebremariam YT, LePendu P, Lee JC, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. Circulation 2013;128:845–853
11. Landi SN, Sandler RS, Pate V, Lund JL. No increase in the risk of acute myocardial infarction in privately insured adults prescribed proton pump inhibitors vs histamine-2 receptor antagonists (2002-2014). Gastroenterology 2018; 154:861– 873
12. Nguyen LH, Lochhead P, Joshi AD, et al. No significant association between proton pump inhibitor use and risk of stroke after adjustment for lifestyle factors and indications. Gastroenterology 2018; 154:1290–1297
13. Sauvet P, Schouler L. Omeprazole and liver functions. Rev Med Interne 1992;13: 359 – 363
14. Steinijans VW, Huber R, Hartmann M, Zech K, Bliesath H, Wurst W, Radtke HW. Lack of pantoprazol drug interactions in man: an updated review. Int J Clin Pharma- col Ther 1996;34:243 – 262
15. Sampathkumar, Ramalingam et al Acute Interstitial Nephritis due to proton pump inhibitors.Indian J Nephrol 2013.23(4) 304
16. Muriithi AK et al. Biopsy proven acute interstitial nephritis. Am J Kidney disease.2014;64(4) 558
17. Xie Y, Bowe B, Li T, et al. Proton pump inhibitors and risk of incident CKD and progression to ESRD. J Am Soc Nephrol 2016; 27: 3153–3163
18. Hess MW et al, Systematic review: Hypomagnesemia induced by proton pump inhibitors.Aliment Pharmacol Thera 2012, Sep 36(5) 405- 413
19. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivali N, Edmonds PJ, Ungprasert P, O'Corragain OA, Korpaisarn S, Erickson SB, Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Ren Fail. 2015;37(7):1237
20. Recker RR ,Calcium absorption and achlorhydria.N Engl J Med. 1985;313(2):70
21. Yang YX, Lewis JD, Epstein S, et al. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006;296:2947–2953
22. Targownik LE, Leslie WD, Davison KS, et al. The re-

lationship between proton pump inhibitor use and longitudinal change in bone mineral density: a population-based study [corrected] from the Canadian Multicentre Osteoporosis Study (CaMos). Am J Gastroenterol 2012;107:1361–1369

23. Ajmera AV, Shastri GS, Gajera MJ, Judge TA, Suboptimal response to ferrous sulfate in iron-deficient patients taking omeprazole.Am J Ther. 2012;19(3):185

24. Badiola N, Alcalde V, Pujol A, et al. The proton-pump inhibitor lansoprazole enhances amyloid-beta production. PLoS One 2013;8:e58837

25. Haenisch B, von Holt K, Wiese B, et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. Eur Arch Psychiatry Clin Neurosci 2015;265:419–428

26. Gomm W, von Holt K, Thome F, et al. Association of Proton Pump Inhibitors With Risk of Dementia: A Pharmacoepidemiological Claims Data Analysis. JAMA Neurol 2016;73:410–416

27. Bavishi C, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. Aliment Pharmacol Ther 2011;34: 1269–81

28. FuruyaKanamori L, Stone JC, Clark J, et al. Comorbidities, exposure to medications, and the risk of community-acquired Clostridium difficile infection: a systematic review and meta-analysis. Infect Control Hosp Epidemiol 2015;36:132–141

29. Freedberg DE, Lamouse-Smith ES, Lightdale JR, et al. Use of Acid Suppression Medication is Associated With Risk for C. difficile Infection in Infants and Children: A Population-based Study. Clin Infect Dis 2015;61:912–917

30. Xu HB, Wang HD, Li CH, et al. Proton pump inhibitor use and risk of spontaneous bacterial peritonitis in cirrhotic patients: a systematic review and meta-analysis. Genet Mol Res 2015;14:7490–7501

31. Lambert AA, Lam JO, Paik JJ, et al. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PLoS One 2015;10:e0128004

32. Laheij RJ, Sturkenboom MC, Hassing RJ, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA 2004;292:1955–1960

33. Sarkar M, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. Ann Intern Med 2008;149:391–398

34. Scheiman JM, Devereaux PJ, Herlitz J, et al. Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomized, controlled trial (OBERON). Heart 2011;97:797–802

35. Estborn L, Joelson S. Frequency and time to onset of community-acquired respiratory tract infections in patients receiving esomeprazole: a retrospective analysis of patient-level data in placebo-controlled studies. Aliment Pharmacol Ther 2015;42:607–61339.

36. Krag M, Perner A, Wetterslev J, et al. Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomized clinical trials with meta-analysis and trial sequential analysis. Intensive Care Med 2014;40:11–2240.

37. ar ıa r ıguez LA, Lagergren J, Lindblad M. Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case-control study in the UK. Gut 2006;55:1538–44

38. Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. Gastroenterology 2019;157:682–691

39. Inadomi JM, Fendrick AM. PPI use in the OTC era: who to treat, with what, and for how long? Clin Gastroenterol Hepatol. 2005;3:208–215

40. Savarino V, Dulbecco P, De Bortoli N, et al. The appropriate use of proton pump inhibitors (PPIs): the need for a reappraisal. Eur J Intern Med. 2017;45:160–168

41. Vincezo S, Elisa M et al, Proton Pump Inhibitors: Use and Misuse in clinical settings.Expert Review of Pharmacology.2018 (11);1123-1134

Dr. Thachil A*, Dr. Jose J, Dr. Mathew R,
Dr. Abdullakutty J, Dr. Joseph J, Dr. George J, Dr. Saji N C
Lisie Heart Institute, Lisie Hospital,
Correspondence: docthachil@hotmail.com

EP Session

PERINODAL ATRIAL TACHYCARDIA: A CASE-BASED DISCUSSION

Case Summary.

A 72-year-old hypertensive lady on treatment with Metoprolol presented with sustained palpitation. She reported multiple similar episodes in the past. Her blood investigations and echocardiogram were unremarkable. Figure 1 shows her ECG at presentation, and Figure 2 shows the ECG during the administration of 6 mg of Adenosine. What are the likely possibilities?

Management.

An electrophysiology study was performed, during which time the tachycardia started spontaneously (Figure 3). The study revealed a focal atrial tachycardia originating from the perinodal tissue just posterosuperior to the apex of the Koch's triangle (Figures 4 and 5). Radiofrequency ablation (RFA) from the noncoronary cusp was unsuccessful, following which successful RFA was performed from the right septal aspect just posterosuperior to the apex of the Koch's triangle without complications (Figure 6). The same dose of Metoprolol was continued after RFA, without additional antiarrhythmic drugs. The patient has remained asymptomatic over the next three months of follow up.

Discussion.

The ECG at presentation (Figure 1) shows a regular narrow QRS tachycardia with a 1:1 AV relationship. The RP: PR interval is > 1. This pattern is compatible with an atrial tachycardia (AT) with 1:1 AV conduction, a fast-slow atrioventricular nodal re-entrant tachycardia (AVNRT), or an orthodromic atrioventricular re-entrant tachycardia mediated by an accessory pathway with slow retrograde conduc-

tion. The P waves (arrows) are negative in leads II, III, aVF, positive in leads aVR and aVL, and nearly isoelectric in lead I. This localizes the tachycardia to the inferior part of the atria adjacent to the midline. The P waves are not clearly visible in the chest leads, particularly in V1. This makes it difficult to localize the tachycardia to either the anterior (right) or the posterior (left) atrium and suggests a site of origin between the right and the left atria. The P waves during tachycardia are narrower (70 ms) than the sinus P waves (110 ms), suggesting that the tachycardia originates from a vantage point that can rapidly activate both the atria as compared to the site of origin of the sinus impulse. In a long RP tachycardia with 1:1 AV association, it is not possible to differentiate between atrial tachycardia, AV nodal re-entrant tachycardia and orthodromic atrioventricular re-entrant tachycardia based on the ECG during tachycardia, especially when the P waves are negative in the inferior leads. Positive P waves in the inferior leads would rule out AV nodal re-entrant tachycardia but are compatible with an accessory pathway inserting in the superior parts of the atrium or atrial tachycardia.

ECGs recorded during onset (Figure 3) and/or termination (Figure 2) of tachycardia can give further clues. Observations to be made on the ECG during the onset of tachycardia are discussed along with Figure 3. An atrial or ventricular ectopic beat terminating the tachycardia often makes further analysis regarding the mechanism of tachycardia unreliable. In this case, Adenosine terminates the tachycardia without causing an ectopic beat before termination. The last beat of the tachycardia is a QRS complex. Thus, Adenosine terminates the tachycardia by preventing the occurrence of the atrial activity. If a vagal maneuver or Adenosine terminates the tachycardia without ectopy, and the last recorded complex is a QRS, an orthodromic atrioventricular re-entrant tachycardia is very unlikely. The mechanism of tachycardia termination in such a situation is either a block in retrograde (VA) conduction via the AV node, which would be expected to terminate AV nodal re-entrant tachycardia, or suppression of Adenosine sensitive atrial tachycardia by the drug. If a vagal maneuver or Adenosine terminates the tachycardia without ectopy, and the last recorded complex is a P wave, atrial tachycardia is very unlikely. The mechanism of tachycardia termination in such a situation is a block in antegrade AV conduction via the AV node, which would be expected to terminate AV nodal re-entrant tachycardia and orthodromic atrioventricular re-entrant tachycardia but not affect atrial tachycardia.

Adenosine usually suppresses or terminates focal atrial tachycardias due to triggered activity or automaticity, and sinus node reentrant tachycardia, but does not affect macro reentrant atrial tachycardia/atrial flutter. 1-2 Some reports suggest that Adenosine does not affect micro reentrant atrial tachycardias 3. Adenosine also terminates most AV nodal reentrant tachycardias and atrioventricular re-entrant tachycardias. Thus, termination during the administration of Adenosine does not differentiate atrial tachycardia from AV nodal re-entrant tachycardia or atrioventricular re-entrant tachycardia. Continuation of atrial arrhythmia during Adenosine induced AV block differentiates atrial tachycardia from AV nodal dependent tachycardias, but this is expected to happen reliably only in macro re-entrant atrial tachycardias. Thus, response to Adenosine has only a modest role in differentiating an atrial tachycardia of unknown mechanism from AV node dependent supraventricular tachycardia. 4

Perinodal atrial tachycardia (often called paraHisian or noncoronary cusp or paraseptal atrial tachycardia, and sometimes included under the group of Koch's triangle atrial tachycardias or anterior septal atrial tachycardias) arises from the tissue adjacent to the apex of the Koch's triangle. The tissue responsible for the arrhythmia is often located in the fibrous body between the noncoronary cusp of the aorta and the apex of the Koch's triangle.5 Some investigators consider this tissue to be a remnant of the embryonic retro aortic AV node.5 The P waves originating from this area are usually negative in leads II, III, aVF, positive in aVL, biphasic in V1 (rather than the isoelectric P wave in this example), and narrower than the sinus P waves of the same patient. 6-7 However, no "signature" P wave morphology has been associated with origin from this site, perhaps due to the variability in exit that a tachycardia originating from this site can take.5 Perinodal ATs are invariably Adenosine and Verapamil sensitive.5,8 Adenosine and Verapamil sensitivity, though, is not a feature unique to perinodal AT; ATs from other sites, notably periannular ATs have been shown to exhibit Adenosine and Verapamil sensitivity.9 Perinodal AT shows a female preponderance, presents as paroxys-

mal AT, and usually occurs for the first time in middle age with subsequent increase in frequency.5

RFA is superior to medical therapy for the management of AT in structurally normal hearts. In, experienced centers, when the AT can be induced in the laboratory, acute success rates of above 90-95% have consistently been reported, with a complication rate of <1% to 2%.4 Thus, current guidelines recommend RFA as a Class I indication for long term management of AT in structurally normal hearts. Oral beta-blockers, diltiazem, or verapamil are reasonable for ongoing management in patients with symptomatic focal AT. These drugs are moderately effective, with a low incidence of significant adverse effects, and are accordingly given a Class IIa indication for the management of AT.

Combinations of a class Ic drug (Flecainide or Propafenone) with a beta-blocker, diltiazem, or verapamil may improve overall efficacy rates. This combination requires closer monitoring and is also accorded a Class IIa indication for the management of AT. Class III drugs (Amiodarone, Sotalol) are also moderately effective in suppressing focal AT. Because of the risk of proarrhythmia and other complications, before the use of these drugs, a balance between the anticipated benefit of focal AT suppression and the potential adverse effects of these drugs should be carefully considered. These drugs are therefore given a Class IIb indication in the management of focal AT.4

The tissue responsible for perinodal AT is usually ablated from the noncoronary cusp of the aorta.10 The noncoronary cusp simply offers a vantage point of access to this tissue and does not harbor the arrhythmogenic tissue per se. In occasional cases, ablation from the right septal or left side (from the region of the aortomitral continuity) may be required.10 With meticulous mapping and careful energy titration, this area can be ablated with a high degree of success (99%) without causing damage to the AV nodal inputs (< 1% complication rate).6

Figures

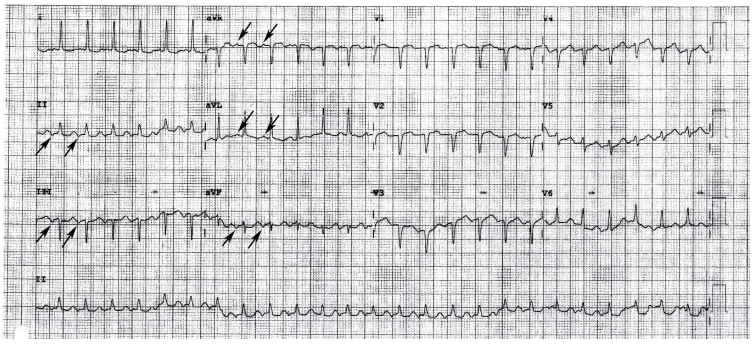


Figure 1. Tachycardia at presentation. The black arrows show P waves which are negative in II, III, a VF and positive in aVR, aVL. The RP interval is > PR interval.

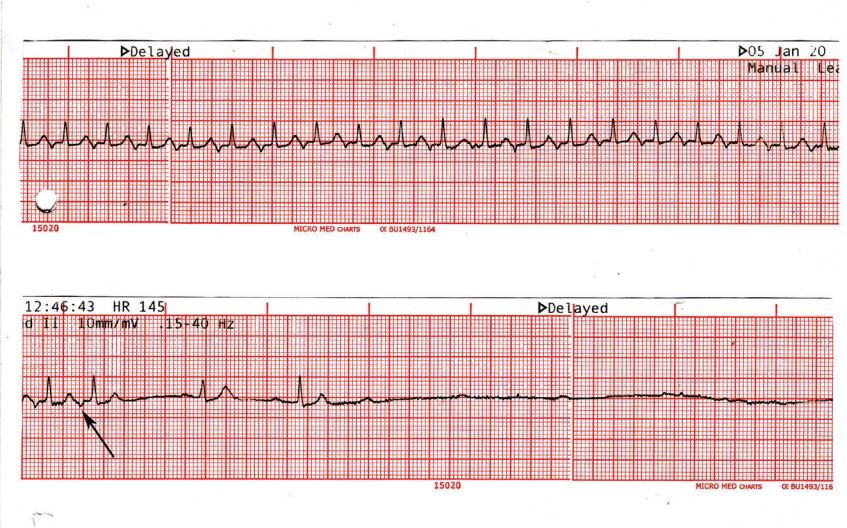


Figure 2. ECG recorded during the administration of Adenosine. Tachycardia terminates with a QRS complex. The last P wave of the tachycardia is marked (arrow). This implies termination due to either Adenosine induced VA block in an AV node dependent re-entry, or cessation of an Adenosine sensitive atrial tachycardia. Note that the P wave during tachycardia is 70 ms in duration, compared to the sinus P wave of 110 ms duration.

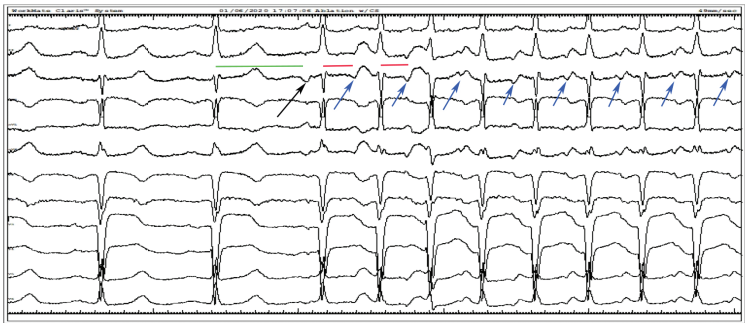
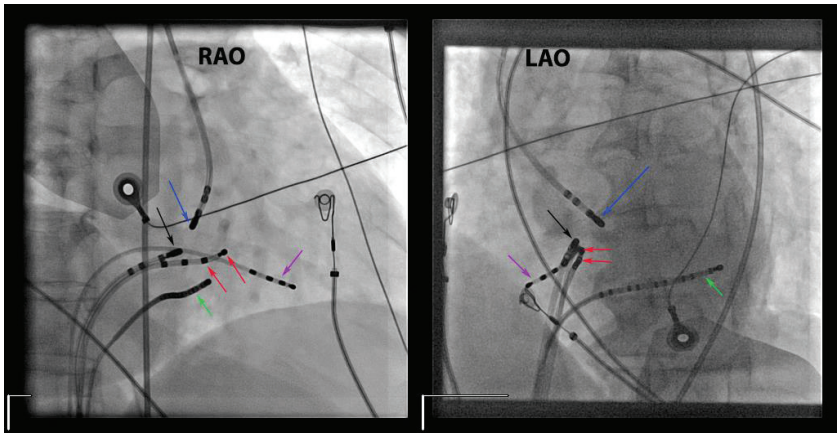


Figure 3. Spontaneous onset of tachycardia during EP study.
The onset of tachycardia is marked by the black arrow. The RP interval preceding the first beat of tachycardia (green line) is different from the RP intervals during the tachycardia (red lines). This suggests that a change in VA conduction (as in AV nodal reentrant tachycardia or orthodromic atrioventricular re-entrant tachycardia) is NOT critical to initiating the tachycardia. The tachycardia thus starts spontaneously with a P wave (black arrow). The first P wave of the tachycardia (black arrow) is similar to all the other P waves of the tachycardia (blue arrows). There is no ectopic P wave initiating the tachycardia. This is consistent with either a tachycardia initiated and perpetuated by a change in VA conduction (which was refuted by the previous explanation), or an atrial tachycardia arising from a small area (as in a focal or micro re-entrant atrial tachycardia) rather than an atrial tachycardia due to a large re-entrant circuit (in which an initiating ectopic P wave would enter a large circuit, and come out of the circuit as the tachycardia P wave, often of a morphology different from the initiating P wave).

Figure 4. Catheter placements during electrophysiology study depicting the site of origin of the tachycardia. Colored arrows indicate the following catheters. Black = ablation catheter in the Koch's triangle (site of ablation). Red = catheter recording His bundle deflection at the apex of the Koch's triangle (from the distal bipole). Blue = catheter in the noncoronary cusp of the aorta, just superior to the Koch's triangle. Green = catheter in the coronary sinus. Purple = catheter in the right ventricle. RAO = Right anterior Oblique. LAO = Left Anterior Oblique



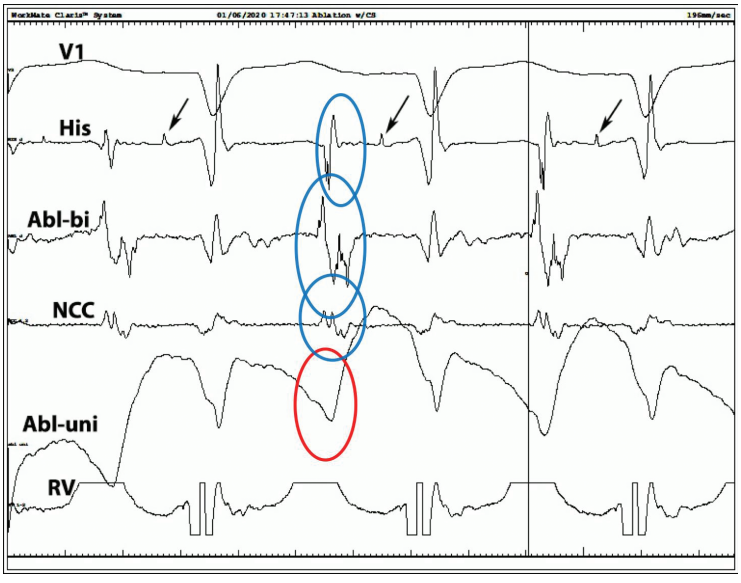


Figure 5. Intracardiac electrograms during atrial tachycardia recorded during the electrophysiology study. Catheter locations during this recording are as shown in Figure 4. Bipolar recordings (which denote local electrical activity from under the recording the bipole) of atrial activity are circled in blue. The earliest electrical activity is recorded by the ablation catheter (Abl-bi), followed by the catheter in the noncoronary cusp (NCC), followed by the catheter recording the His bundle deflection (His; black arrows show the His bundle deflection). The red circle highlighting unipolar recording from the tip of the ablation catheter (Abl-uni) shows a QS deflection, suggesting that all electrical activity flows away from the catheter site; this occurs when the catheter tip is at the source of the tachycardia.

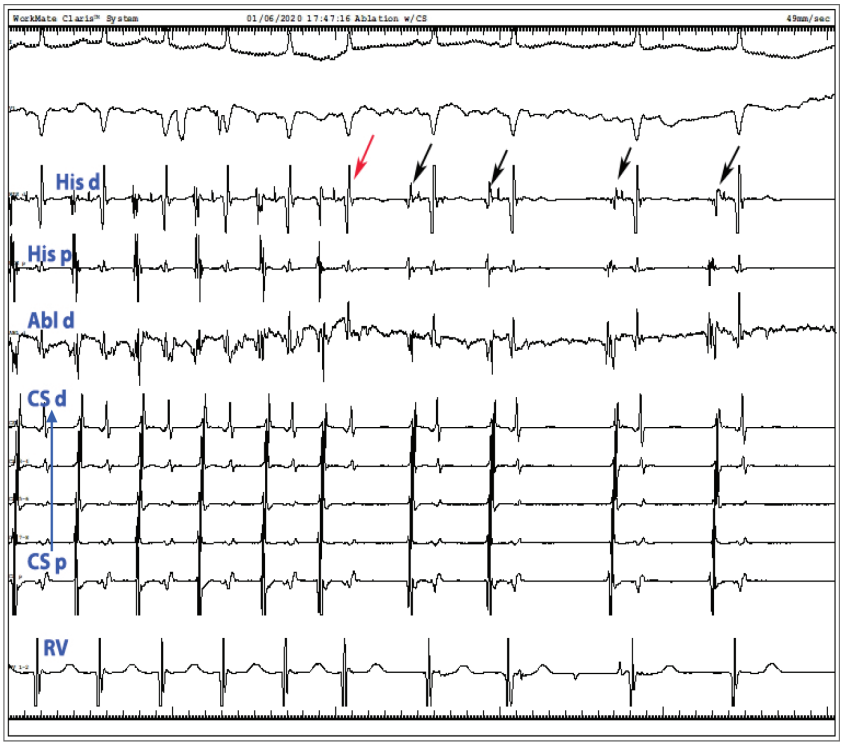


Figure 6. Termination of tachycardia during RFA. The red arrow depicts the last beat of tachycardia. Black arrows show sinus beats after the termination of tachycardia. Catheter locations are as in Figure 4. His d = distal bipole of the His catheter. His p = proximal bipole of the His catheter (note that the His bundle deflection is not recorded by this bipole). Abl d = Ablation catheter. CSp -> CSd = proximal to distal poles of the coronary sinus catheter.

References.

1. Response to Adenosine Differentiates Focal From Macroreentrant Atrial Tachycardia: Validation Using Three-Dimensional Electroanatomic Mapping. Iwai S, Markowitz SM, Stein KM, Mittal S, Slotwiner D J, Das M K et al. Circulation. 2002;106:2793-2799
2. Mechanism - Specific Effects of Adenosine on Atrial Tachycardia. Engelstein E D, Lippman N, Stein KM, Lerman B B. Circulation.1994;89:2645-2654
3. Unifying Algorithm for Mechanistic Diagnosis of Atrial Tachycardia. Liu CF, Cheung J W, Ip J E, Thomas G, Yang H, Sharma S et al. Circ Arrhythm Electrophysiol. 2016;9:e004028
4. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Page R L, Joglar J A, Caldwell M A, Calkins H, Conti JB, Deal B J et al. Heart Rhythm 2016;13:e136–e221
5. Reappraisal and new observations on atrial tachycardia ablated from the non-coronary aortic sinus of Valsalva. Bohora S, Lokhandwala Y, Sternick E B, Anderson R H, Wellens H J J. Europace (2018) 20, 124–133
6. Ablation of focal atrial tachycardia from the non-coronary aortic cusp: case series and review of the literature. Beukema R J, Smit J J J, Adiyaman A, Casteren L V, Delnoy P P H M, Misier A R R et al. Europace (2015) 17, 953–961
7. P-Wave Morphology in Focal Atrial Tachycardia: Development of an Algorithm to Predict the Anatomic Site of Origin. Kistler PM, Roberts-Thomson KC, Haqqani HM, Fynn S P, Singarayar S, Vohra J K, et al. J Am Coll Cardiol 2006;48:1010–7
8. Analysis of the Anatomical Tachycardia Circuit in Verapamil-Sensitive Atrial Tachycardia Originating From the Vicinity of the Atrioventricular Node. Yamabe H, Tanaka Y, Morihisa K, Uemura T, Enomoto K, Kawano H et al. Circ Arrhythm Electrophysiol. 2010;3:54-62
9. Electrophysiologic Characteristics of Verapamil-Sensitive Atrial Tachycardia Originating from the Atrioventricular Annulus: Yamabe H, Tanaka Y, Okumura K, Morikami Y, Kimura Y, Hokamura Y et al. Am J Card. 2005; 95(12): 1425-1430
10. Focal Atrial Tachycardia Surrounding the Anterior Septum: Strategy for Mapping and Catheter Ablation. Wang Z, Ouyang J, Liang Y, Jin Z, Yang G, Liang M et al. Circ Arrhythm Electrophysiol. 2015;8:575-582

Dr. J.Raghav*
Dr. G.Ashok#**
Dr. Durgadevi**
Correspondence: dr.g.ashok@gmail.com

Original Article

SERUM COPEPTIN LEVEL AND TROPONIN 'I' IN ACUTE MYOCARDIAL INFARCTION FOR EARLY DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

Abstract

Aims and objectives:

To evaluate the usefulness of copeptin levels in the diagnosis of acute coronary syndromes(ACS) when used in combination with cardiac troponin I (cTnI) in patients presenting to the casualty with typical cardiac chest pain.

Methods:

89 patients were enrolled in the study. 59 patients had Acute Coronary Syndrome (ACS) with chest pain duration of < 6 hours and 30 had no clinical symptoms. Baseline history and clinical examination were done. Serum copeptin, cardiac troponin I, CKMB and baseline routine investigations were sent to our central laboratory. Results were analyzed to see if Serum Copeptin levels add any incremental data to the existing cardiac biomarkers.

Results:

A total of 59 patients with ACS were included in the study. The mean age of the study population was 55.75 ± 10.57. Of the study population, 46 were male and 13 were females. Also, 26 were ASMI, 19 were IWMI, 13 NSTEMI and the rest were Unstable angina. Copeptin of >14pg/ml was taken as abnormal. In our study of patients with chest pain presenting within 6 hours, the sensitivity of copeptin with troponin is 89.83% and specificity is 90%, and negative predictive value 98.78%. Association between troponin I and Copeptin in patients presenting with chest pain within 6 hours were found to be statistically significant with a p-value of 0.0001.

*Resident,** Assistant Professor, Department of Cardiology, Chettinad hospital and research institute, Chennai.

Conclusions:

In patients presenting with chest pain, serum copeptin levels in combination with troponin I provide a high negative predictive value. It will help in making an early decision and safely ruling out ACS.

Keywords: Acute coronary syndromes(ACS), Troponin I, Copeptin.

Introduction:

Myocardial ischemia can occur if there is inadequate blood supply to the myocardium. When ischemia is prolonged, it can lead to myocardial infarction producing acute coronary syndrome. Acute coronary syndromes can be either ST-elevation myocardial infarction (STEMI), non ST elevation myocardial infarction (NSTEMI) or unstable angina.

The most common and useful biomarker for the diagnosis of acute coronary syndromes is cardiac troponin. Now quantitative assays of cardiac troponin are available for early diagnosis of acute coronary syndromes. The drawback of these quantitative assays is that these tests can be negative in the initial 2 hours of acute coronary syndrome. Thus there is a need for a new biomarker for early and confirmatory diagnosis of acute coronary syndromes especially for NSTEMI and unstable angina in whom, the ECG may be unremarkable and cardiac troponin may be negative in the first few hours.

Serum copeptin is found to be elevated in patients with acute MI. Though a nonspecific marker, the combination of copeptin with troponin I might allow for early and rapid diagnosis or early rule out of acute coronary syndromes without serial blood sampling.

Materials and Methods:

The present study was carried out in the Department of Cardiology, Chettinad Hospital and Research Institute, Chennai a super specialty tertiary care teaching hospital attached to Chettinad Academy of Research and Education, Chennai.

The study was done over a period of 1 year with 89 participants. Patients presenting to the casualty with chest pain duration < 6hour were taken into the study. Patients were selected by a simple random sampling method.

59 subjects who were admitted in the Intensive Coronary Care Unit with complaints of chest pain duration less than 6 hours and confirmed diagnosis of ACS were enrolled as the study group. Patients were diagnosed as Acute Coronary syndrome based on history, presenting ECG, echocardiogram, and biomarkers (Troponin I quantitative analysis, or CKMB). In the case of NSTEMI, if initial troponin I was negative at presentation, repeat troponin I was sent 12 hours later to confirm the diagnosis. The acute myocardial infarction as defined by the Third Universal Definition of Myocardial Infarction.

Inclusion Criteria:

All patients more than 18 years of age with:

1. Typical cardiac chest pain (i .e, retrosternal compressing chest pain on exertion or rest pain lasting for more than 20 minutes) associated with or without ECG changes.
2. Duration of chest pain less than 6 hours

Exclusion criteria:

1. Patients younger than 18 of years
2. Atypical chest pain at presentation
3. Patients with features of Sepsis
4. Patients in Shock
5. Patients with coexisting end-stage renal disease or end-stage liver disease
6. Recent cerebrovascular accidents
7. Patients with peripheral artery disease
8. Preeclampsia

30 subjects with normal clinical, biochemical parameters and normal ECG who were selected from the master health check-up outpatient department of Chettinad Hospital and Research Institute served as the control group.

For the laboratory measurement of copeptin, 2 mL of whole venous blood was obtained from patients on admission. The samples were centrifuged at 3000 rpm for 10 minutes to separate the serum. Samples were stored at -80°C until analysis.

Measurements of cTnI were done using Beckman coulter Access Accu TnI assay and Creatine kinase-MB isoenzyme (CK-MB) was performed using the Modified IFCC method.

Estimation of copeptin was done using Qayee Bio Elisa Copeptin Kit. The standard cure provided with the kit was used to interpret the values.

Statistical Analysis

The collected data were analyzed using statistical package for social science (SPSS version 21.0), Medcalc Statistical software (version 18.11.3). The qualitative data were expressed in proportion. Chi-square test was used for qualitative variables in which $p<0.05$ were considered statistically significant. Mean and the standard deviation was calculated for all the quantitative values. Percentages and numbers were used to denote qualitative variables. ROC curve (receiver operator characteristic) was plotted for estimating out the best cut -off value. Sensitivity and specificity tests were also done.

Results:

In this study, the total sample size was 89 (59 study population and 30 controls). Demographic variables, serum copeptin, troponin I and CKMB were analyzed. There were a total of 59 patients with ACS in the study. The patient's age ranged from 29 to 80 years. The mean age of the study population was 55.75 ± 10.57. Of the study population, 46 were male and 13 were females. Among the control group, the mean age of the participants was 52.23 ±13.42. 17 were males and 13 were females. (Table 1)

Table 1: Distribution of the patient population in the study (n=89)

	Cases			Control		
Variable	Number	Percentage	Mean ± S.D	Number	Percentage	Mean ± S.D
Age	29-80	-	55.75 ± 10.57	27-77	-	52.23±13.42
Gender						
Male	46	78%		17	56.7%	
Female	13	22%		13	43.3%	

26 patients had ASMI, 19 had IWMI, 13 had NSTEMI and 1 patient had Unstable Angina. (Table 2).

Table 2: Distribution of study participants with ACS based on diagnosis (n=59)

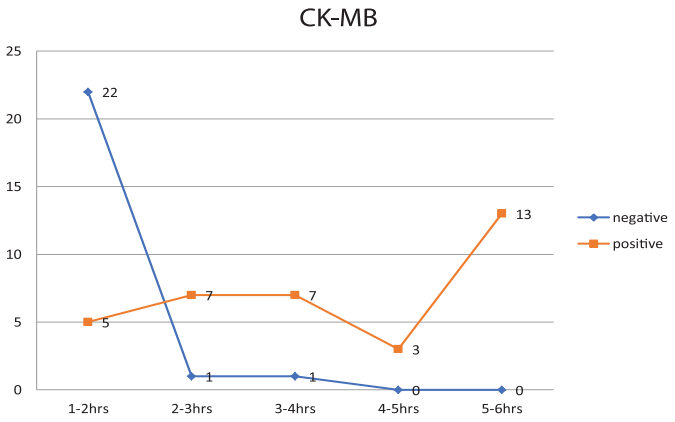
Diagnosis	Frequency	Percent
ASMI	26	44.1
IWMI	19	32.2
NSTEMI	13	22.0
UA	1	1.7
Total	59	100.0

markers (n=59)

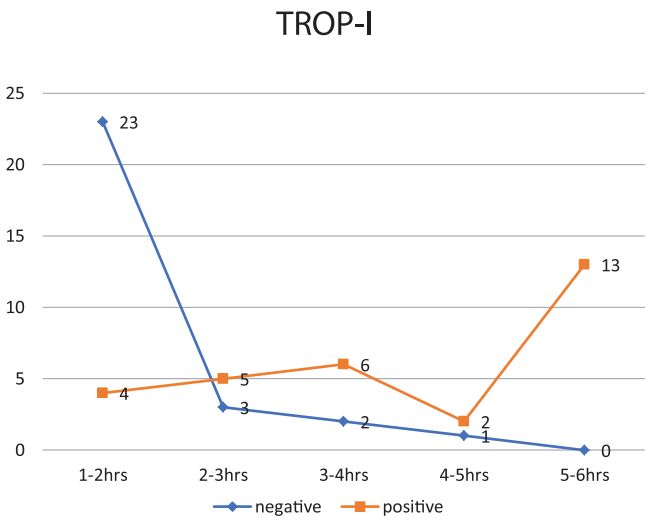
Diagnostic Marker	Frequency	Percentage	
Copeptin			
<14 (ng/ml)	6	10.2%	34.54 ± 25.09
>14 (ng/ml)	53	89.8%	
CKMB			
>25 (U/L)	24	40.7%	36.97 ± 24.08
<25(U/L)	35	59.3%	
TROPONIN I			
<0.01 (ng/ml)	29	49.2%	

Serum copeptin was found to be normal in 6 patients while the remaining 53 patients had high serum copeptin levels. CKMB was positive in 24 patients and 35 patients had negative serum levels. Serum troponin was elevated in 30 patients and negative in 29 patients.(Table 3)

CKMB was negative in 22 patients and positive in 5 patients with chest pain duration of 1-2 hours. It was negative in 1 patient and positive in 7 patients with chest pain duration of 2-3 hours. In patients with chest pain lasting 3 to 4 hours, 1 patient had negative values and 7 patients had positive values. CKMB was found to be positive in 3 patients at 4-5 hours and in 13 patients at 5-6 hours. So in the initial 1-2 hours, many patients with acute coronary syndromes can have negative values and hence missed.(Graph 1)



Graph 1: The number of patients with positive and negative CK-MB levels and duration of chest pain



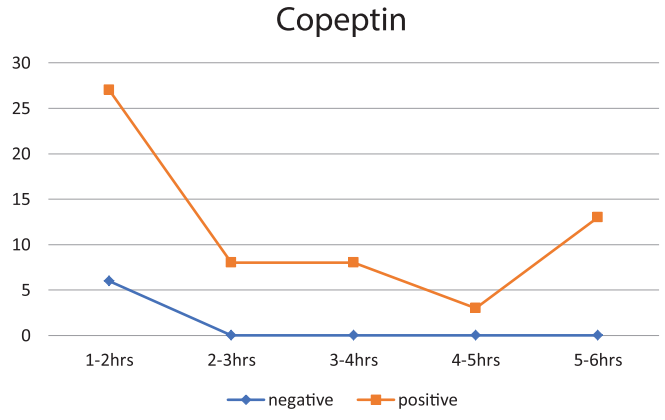
Graph 2: The number of patients with positive and negative troponin I levels and duration of chest pain

The X-axis shows the duration of chest pain and the Y-axis the number of patients

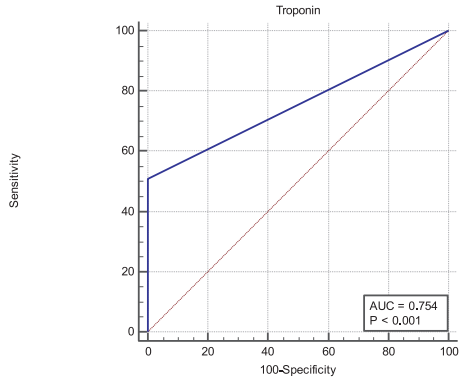
At 1-2 hours of chest pain, 23 patients had negative troponin levels and only 4 had positive troponin levels. Of all patients presenting with 2-3 hours of chest pain, 5 had positive troponin levels and 3 had negative troponin levels. In patients presenting with chest pain duration of 3-4 hours, 6 had positive troponin levels and 2 patients had negative troponin levels. Also, 1 patient and 2 patients respectively had negative and positive troponin levels at 4-5 hours of chest pain, at 6 hours, 13 patients had positive troponin levels and none had negative troponin levels. It is observed that in the early hours of myocardial infarction, troponin levels can be deceptively negative. (Graph 2)

The X-axis shows the duration of chest pain and the Y-axis the number of patients

The serum copeptin levels were elevated in the majority of the patients even within the first 2 hours. And was negative only in the first 2 hours in 6 patients(Graph 3)



Graph 3: The number of patients with positive and negative copeptin levels and duration of chest pain

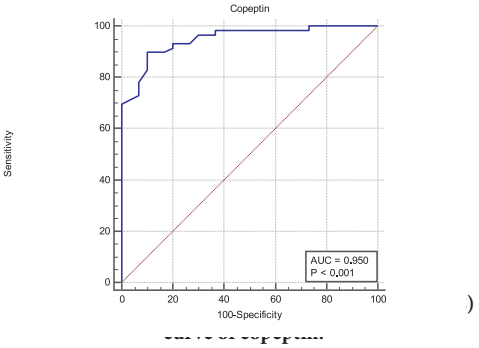


AUC	CI	SENSITIVITY	SPECIFICITY	NPV	p-value
75%	0.65 to 0.83	50.85%	100%	95.73%	P=<0.0001

Graph 4: The receiver operator characteristic (ROC) curve of troponin I

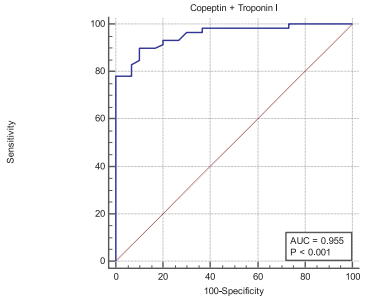
ROC curve was plotted for serum troponin I as a predictive marker of acute myocardial infarction in patients presenting with chest pain duration less than 6 hours. The AUC for troponin to predict acute myocardial infarction was 75% (CI = 0.65 - 0.83). The sensitivity was 50.85% and specificity was 100%. P-value is <0.0001 which is statistically significant. (Graph 4)

P<0.05 were considered statistically significant ROC curve was plotted for serum copeptin as a predictive marker of acute myocardial infarction. The AUC for copeptin to predict acute myocardial infarction was 95% (CI = 0.88–0.98). The sensitivity was 89.83% and specificity was 90% with a cut off of 13.3ng/ml. P-value is <0.0001 which is statistically significant. (Graph 5)



AUC	CI	SENSITIVITY	SPECIFICITY	NPV	p-value
95%	0.88 to 0.98	89.83%	90.00%	98.78%	P=<0.0001

Graph 5: The receiver operator characteristic (ROC) curve of copeptin.



AUC	CI	SENSITIVITY	SPECIFICITY	NPV	p-value
95.5%	0.88 to 0.98	89.83%	90.00%	98.78%	P=<0.0001

Graph 6: The receiver operator characteristic (ROC) curve of combination of Copeptin and Troponin I

ROC curve was plotted for the combination of Troponin I and serum copeptin as a predictive marker of acute myocardial infarction. The AUC for the combination to predict acute myocardial infarction was 95.5% (CI = 0.88–0.98). The sensitivity was 89.83% and specificity was 90%. P-value is <0.0001 which is statistically significant.(Graph 6)

Discussion:

Copeptin is a new endogenous stress marker being evaluated for the diagnosis of acute coronary syndromes. It is elevated in cases of acute coronary syndrome even before troponins are elevated. So there was a profound interest in it as a biomarker for early detection of acute coronary syndromes.

Numerous studies have been done to assess the usefulness of copeptin as a marker for ACS. Some have combined serum copeptin with troponin I for rule in or rule out of ACS for patients presenting early with chest pain to casualty.

The CHOPIN trial was a large multicenter trial done on patients presenting with chest pain. Of all the patients, only 8% had confirmed diagnosis of AMI (STEMI, NSTEMI), and about 60% had chest pain that was non-cardiac in origin. From their trial, it was found that by adding Copeptin among patients who presented with non-diagnostic ECG, 58% could be ruled out. So there was a 43% reduction in time to diagnosis of ACS from average 3 to 1.8 hours. Also, it was found out that when both Copeptin and Troponin I were negative at the presentation of symptoms, it had a negative predictive value of > 99% to rule out ACS.1Our study results were similar to that of the above study in that the combination of serum Copeptin to troponin I had a NPV of 98.78%.

In a study by Reichlin and Mueller et al.2 patients presenting to the casualty with chest pain were studied. In their study, most patients presenting early<4 hours had a negative troponin, while Copeptin was elevated. They concluded that Copeptin as a single variable has only a modest accuracy for ACS. But the addition of Copeptin to Troponin increases the accuracy but more importantly increases the NPV for ruling out ACS. Our results were also in line with the above study in that the troponin I was negative in many patients during the first 2-3 hours while copeptin was elevated from the first hour itself.3

In Reichlin et al. Study, patients who presented with chest pain were subjected to measurements of Cardiac troponin-T, CKMB, serum myoglobin, and serum copeptin levels serially first at presentation, followed by measurements at third, sixth and ninth hours. It was observed that Copeptin levels were more than Troponin T at presentation. Almost 35% of patients at the time of presentation had undetectable cardiac troponin-T levels. With a combined serum Copeptin assay <14.0 pmol/L and cardiac troponin T levels <0.01ng/ml, ACS was ruled out with a sensitivity of 98.8%, a specificity of 77.1%, NPV of 99.7% and positive predictive value of 46.2%. So adding copeptin helped in early rule out of ACS without the need for prolonged monitoring and repeat Troponin measurement.3

Our study participants were patients with chest pain duration less than 6 hours. It was found that combining Copeptin to Troponin had a sensitivity of 89.83% and specificity of 90% and an improved negative predictive value of 98.78%. Thus the combination of these tests would be helpful in effectively ruling out ACS if both Troponin I and Copeptin were negative at presentation.

Bohyn et al studied Copeptin as an early rule-out strategy in ACS. About 247 patients were included in the study. ACS was found in 50 patients (20.4%). The NPV of combined HS-TnT, copeptin and GRACE score was 99%. They concluded that a negative copeptin and a negative HS-TnT and a low GRACE score in a patient presenting with chest pain fastened the exclusion of ACS.4 Our study results were also similar to the above study but GRACE score was not included.

In a study by Walid Omar et al, 40 patients who presented to the hospital with a history suggestive of ACS were included in the study. Copeptin and troponin assays were done. The primary outcome was AMI. In their study, negative copeptin and negative troponin-I at presentation ruled out AMI with a NPV of 100%. Copeptin >15.6 pg/ml in first 6 h from onset of chest pain picked up AMI patients who were missed by troponin assays.5

In our study, the ROC curve for copeptin plotted had an area under the curve of 95%. The cutoff of copeptin was 13.3ng/ml. Also, copeptin evaluation had a sensitivity of 89.83, Specificity of 90%. The negative predictive value was 98.78%. It was also found to be statistically significant with a p-value of <0.0001. This was in line with that of Walid Omar et al who had an AUC of 98%. Their cut off was 21.1pg/dl in their study, the sensitivity of copeptin was 100%, with a specificity of 87.1%.

A study by Folli, Christian et al., 472 patients were taken in the study. 99 patients had ACS(STEMI, NSTEMI, and UA). In their study, serum copeptin was elevated in STEMI and NSTEMI and not much elevated in UA. Combining copeptin and troponin-T had a NPV of 86.6% for ACS. Our study was much smaller and was done in only 59 ACS patients and 30 normal subjects, we got NPV of 98.78% when combined with

troponin I. In our study, copeptin was also elevated in patients with unstable angina.6

Sebbane, Mustapha et al studied the combination of highly sensitive troponin assay and ultrasensitive copeptin in 194 patients presenting with chest pain < 12 hours duration. 52 (27%) patients had ACS, 25 patients (13%) had STEMI. Higher levels of hs-cTnT (50 [95% confidence interval, 19-173] ng/L) and, and Ultra sensitive-copeptin (30 [13-113] pmol/L) was found in patients with acute myocardial infarction (P <.05). Combining both markers improved receiver operating characteristic area under the curve significantly (from 0.89 [0.85-0.92] for hs-cTnT alone to 0.93 [0.89-0.97], P= .018). Sensitivity and NPV increased, especially for NSTEMI patients (sensitivity, 76% [54.9-90.6] to 96% [79.6-99.9]; NPV, 95% [90.4-98.3] to 98.9% [94.2 to 100]).7 Our study also showed similar results but was done in patients with chest pain duration less than 6 hours. In our study, the sensitivity of Troponin alone to a combination of Serum copeptin and troponin increased from 50% to 89.83% and the NPV increased from 95.73% to 98.78%.

Keller et al also studied copeptin for early diagnosis of AMI. They concluded in their study that Combined copeptin and troponin analysis remarkably improved the NPV virtually independent of onset of chest pain. Also, the copeptin cut off value was studied in a large population study (n =1386). The 99th percentile cut off value was 18.9 pmol/l, the 97.5th percentile 13 pmol/l, and the 95th percentile 9.8 pmol/l. Most of the trials used a cut off value of 14 pmol/l. Lower cut off values of copeptin would yield higher NPVs.2

Conclusion:

In patients presenting with chest pain, serum copeptin levels in combination with troponin-I provide a high negative predictive value. It will help in making an early decision and safely ruling out ACS.

References:

1. Maisel A, Mueller C, Neath SX, et al. Copeptin helps in the early detection of patients with acute myocardial infarction: primary results of the CHOPIN trial (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction). J Am Coll Cardiol. 2013;62:150–160.
2. Keller T, Tzikas S, Zeller T, Czyz E, Lillpopp L, Ojeda FM, et al. Copeptin improves early diagnosis of acute myocardial infarction. J Am Coll Cardiol. 2010;55:2096–106.
3. Reichlin T, Hochholzer W, Stelzig C, Laule K, Freidank H, Morgenthaler NG, et al. Incremental value of copeptin for rapid rule out of acute myocardial infarction. J Am Coll Cardiol. 2009;54:60–8.
4. Emilie Bohyn MD, Elophe Dubie MD, Claire Lebrun MD, Gaspard Beaune MD, PatrickLesage MD, LoïcBelle MD, Dominique Savary MD, Expeditious exclusion of acute coronary syndrome diagnosis by combined measurements of copeptin, high-sensitivity troponin, and GRACE score, The American Journal of Emergency Medicine, Volume 32, Issue 4, April 2014, Pages 293-296.
5. Walid Omar Ahmed, Amr Elmaadawy, Ahmed Yehia, Sameh Elmaraghi, Combined measurements of plasma copeptin and troponin-I levels for the early exclusion of acute myocardial infarction, The Egyptian Journal of Critical Care Medicine, Volume 4, issue 3, 2016, Pages 127-132, ISSN 2090-7303.
6. Folli, Christian et al. Diagnostic role of copeptin in patients presenting with chest pain in the emergency room, European Journal of Internal Medicine, Volume 24, Issue 2, 189 - 193.
7. Sebbane, Mustapha et al. Early rule out of acute myocardial infarction in ED patients: value of combined high-sensitivity cardiac troponin T and ultrasensitive copeptin assays at admission. The American Journal of Emergency Medicine, Volume 31, Issue 9 , 1302 - 1308.

Dr. KP Markose. MD. DM.
Moulana Hospital, Perinthalmanna
Correspondence: drmarkosekp@gmail.com

Review Article

ARTIFICIAL INTELLIGENCE IN CARDIOLOGY

We have seen the different levels of developments in Cardiology from simple pharmacological management to the latest interventional levels. The next development in Cardiology, as in all other aspects of life and science, is the Artificial Intelligence (A.I). A.I is important for Cardiologist with the introduction of data rich technologies such as whole genome sequencing, mobile device biometrics. The robotic implants, home monitoring devices, wearable sensors and mobile apps in health care have produced significant amount of data. The volume of health care data is growing in a rate like 153 Exabytes in 2013 and 2314 Exabytes is expected in 2020 (One Exabyte = 1 billion gigabytes) according to White Paper by Stanford medicine.

An example is the prediction of readmission of a patient with congestive heart failure. This needs analysis of large number of data like Electronic Health Record (EHR) which includes variables like international classification of disease (ICD), Billing codes, medicine prescription, Lab values, Physiological measurements, imaging studies etc. With the help of Machine learning it is easier than human work. So it is time for the Cardiologists to peep into the details of A.I

Artificial Intelligence is the development of intelligent system capable of taking the best possible action in a given situation. Artificial Intelligence consists of **(1) Machine Learning (ML) and (2) Deep learning (DL) - Neural Network.**

The Machine Learning analyse an input data using the different algorithms and define features, Deep learning (Neural network) creates models and make predictions or recommend actions.

Import data → Algorithm → Define features → DL → Create modes → Make predictions or recommendations.

Let us try to understand the Machine Learning and Deep Learning to a little extend.

The Machine Learning

Machine learning needs algorithmically representing data and makes predictions or classifications out of it. For each topic can have different algorithms. There are three main algorithms in ML - Namely -

1) Supervised learning algorithms

2) Un supervised learning algorithms

3) Reinforcement learning algorithms

I. Supervised learning algorithms

This involves classification of an observation into one or more categories or outcomes. Supervised learning algorithm requires data set with predictor variables. This focus on prediction of out come and requires labelled cases - like a teacher that teaches the machine or supervisor as labelled cases. An example is the ECG interpretation LBBB, RBBB / Normal. Another example is that of a study group which investigated the predictive value of supervised ML that incorporated Speckle tracking Echocardiographic data for automated discrimination of HCM from Physiological hypertrophy of heart seen in athletes. The study results showed a positive impact (Narula et al BMJ 2016)

Types of Supervised Learning Algorithm

There are different types of Supervised Learning Algorithms. Let us try to get familiar to some of them:

1) Classification:

A) Binary classification which classifies into two groups like Diabetic / Non-diabetic; Hypertensive / Non-hypertensive etc.

B) Multiple group classification.

2) Regression algorithms

3) Other algorithm

There are two types of regression algorithms.

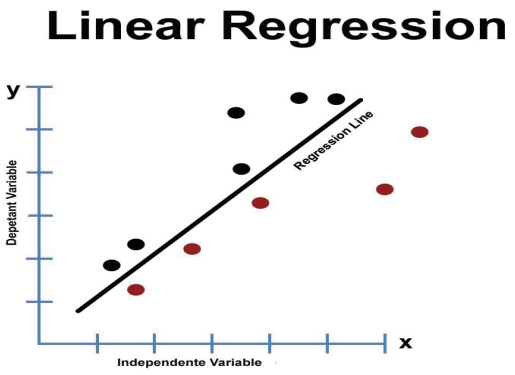
A) Linear regression algorithm

B) Logistic regression algorithm

A) Linear regression algorithm

Here we consider the correlation of two variables

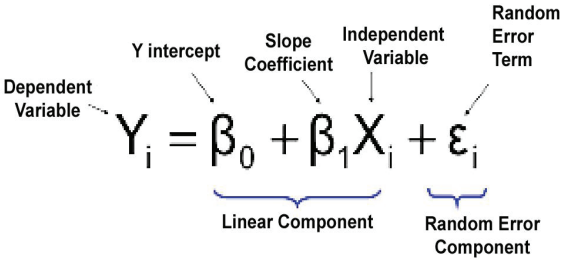
In the linear regression algorithm, there are two variables. One is independent variable which is ploted in X axis and a dependent variable on Y axis. The regression line is drawn through more correlating



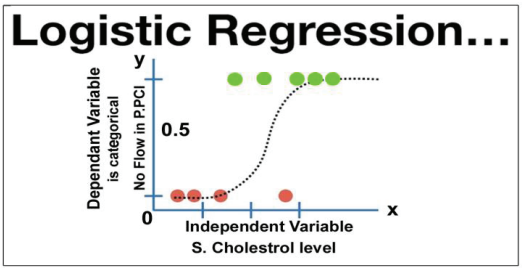
values. From this a dependent value can be found out correlating to the Independent value. For example Hypertension as independent variable and MACE as dependent variable on Y axis. The percentage of MACE can be found out by drawing a Y intercept.

B) Logistic regression algorithm

Logistic algorithm is used for classification. Here also the Independent and dependent variables are there. The independent



variable is ploted on X axis and dependent variable on Y axis. Here the dependent variable is categorical (Binary type variable). This gives the results as Yes or No; Useful or not useful; Pass of Fail etc. Here the Y axis is labelled from 0, 0.5 to one.



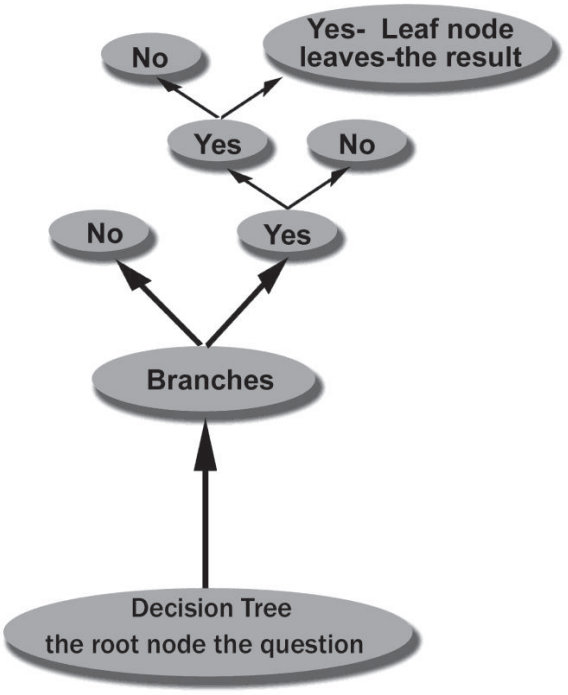
Anything above 0.5 is positive and below that is negative - classify into two. This algorithm calculate the probability. This can be combined to model several class events such as to identify an

image that contains cat or dog and is useful in identifying medical images, events in similar way. Similarly can be combined for Genotype, weight, age etc.

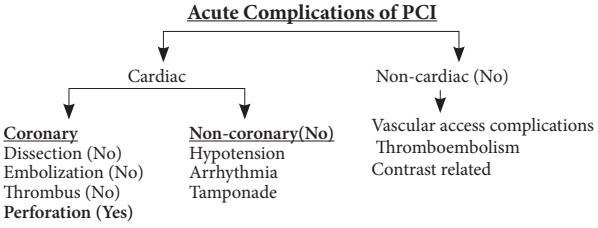
3 other supervised algorithms:

Let us briefly look into them.

A) Decision Tree: This is a type of supervised algorithm. Here we compare the algorithm as a Tree. Here the sample or question is given at the root level. Like the branches of a tree it analyses and at the leaf node level, we get the result.



Example of Decision Tree



The final leaf node outcome is perforation.

B) **Random forest:** This is a group of decision trees. Different specialties with different data regarding a patient with multiple problems (Cardiologist, Nephrologist, Surgeon etc) can have independent tree based algorithm and combining to make a final decision about the patients management.

C) **Support Vector Machine:** In this supervised learning model with associated learning algorithms that analyze data used for classification and regression analysis. An example is the outcome of a study that predicted the ISR with 90% accuracy from plasma metabolite levels (Cuietal - Jacc 2017 - 10)

D) **Regularized regressions:** Regularization means the introduction of additional constraints to decrease the model complexity.

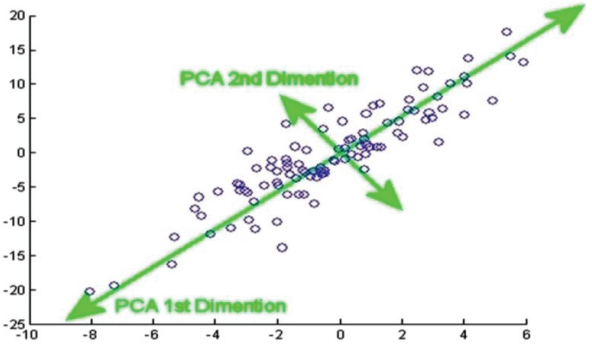
II) Unsupervised learning algorithms:

The unsupervised learning algorithm needs no guides or supervision (No samples). This algorithm tries to discover relationships among variables in data-set. It focus on discovering hidden structures in a data-set by exploring relationship between different variables.

There are two main methods used in unsupervised learning algorithm. They are Principal component analysis (PCA) and Cluster analysis.

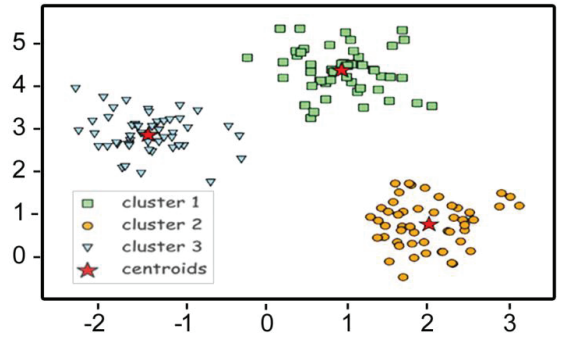
A).Principal component analysis (PCA)

This is the technique used to take a large list of interconnected variables and choose the ones that best suit a model. This process of focusing on only a few variables is called dimensionality reduction and helps to reduce the complexity of the data-set. In other words, it summarizes the data. This algorithm is useful in analyzing of ECG and EEG of Neuro Sciences.



B) Cluster analysis:

In this, algorithm groups with similar nature cluster together. This is used for the classification of objects into relative groups called clusters.



Precision Phenotyping or Precision medicine is the method used to sub-type the disease to a particular group of patient especially for genetic or Molecular profile for more personalized treatment. The Cluster learning algorithm allows to enable precision Cardiology to learn sub-types of many diseases.Most cardiac diseases are slow, heterogeneous, multimorbid, chronic processes where pathogenesis may begin dcades before any disease manifestation. Precision phenotyping in cardiology helps to learn sub types of many diseases and treating them. Thus 3 distinct sub-type were found in Type 2 DM. Using clustering technique, sub-types of heart failure with preserved EF were identified. These are examples of unsupervised learning algorithm.

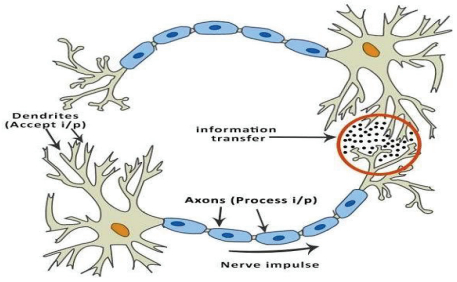
III) Reinforcement Learning Algorithm:

Reinforcement learning algorithm is a type of learning algorithm through trials / by experience. It adapts from hit and trials. It has reward / punishment. Given only the input data an optimized outcome results. Here the models learn the optional method to maximize the final score. This is like a child learning to walk. Playing games and playing chess. This algorithm is useful in doing trials.

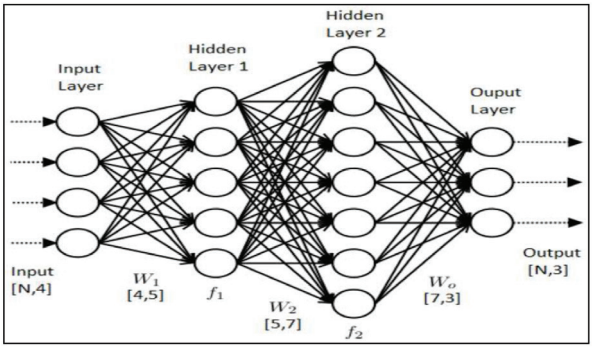
Deep Learning - Neural Network

Deep learning overcomes the limitations in machine learning. This consists of nodes called Neurons arranged in network layout. The neurons resemble biological neurons with dentrictes cell body axon and synapse. These neurons can receive inputs and process the data and transfer to next neuron through synapse.

The first level nodes point into another layer of nodes. There are multiple layers of neuronal nodes called the hidden layers.



The first level nodes points into another layer of nodes. There are multiple layers of neuronal nodes called the hidden layers.



The first neuronal layer is called the input layer. They receive the input data, processes it and transfers to next layer. Then it passes through different hidden layers and reaches the final out put layer as results, recommendations or action.

Two most common forms of deep learning models for supervised learning are

A) Convolutional neural network (CNNS) and

B) Recurrent neuronal network (RNNS)

The difference between CNNS and RNNS is chiefly how layers of neurons are designed. RNNS are well suited for sequential data such as speech and language. RNNS are composed of an additional hidden state vector that contains memory about the history of data previously observed.

Detection of Diabetic Retinopathy, detection of ECG abnormality, classification coronary artery abnormality in Kawasaki with optical coherence tomography images, are some of the studies where CNNS were used.

RNNS was used to predict heart failure diagnosis from EHRS

Concerns

Maintaining the security and privacy of health care data is a concern in A.I. The use of huge volume of data - misusing and possible dangers, behind it is of great concern. The scandal involving Google Deep Mind and Royal Free London NHS foundation trust is an example for the same.

Conclusions

Both AI and Physician can make errors in clinical judgment. A combination of AI and human experience can reduce the clinical errors.

AI supports, rather than replacing the physician.

Dr. Edwin Francis. MD. DM.
Lisie Heart Institute, Lisie Hospital
Correspondence: edifrancis@yahoo.com

Image Challenge:

AN UNFAIR PARTITION

A 28 years old lady presenting with complaints of functional class II symptoms with fatigue and dyspnea on exertion of 6 months duration. Two months before that she had an uneventful surgical closure of atrial septal defect elsewhere via a right infra-mammary approach.

Four months after the surgery she underwent laparoscopic sterilization. Twelve hours after the procedure, she developed left hemiparesis and the CT brain showed a thromboembolic event involving the right middle cerebral artery territory. She was thrombolysed and had a gradual complete recovery. On physical examination, there was mild central cyanosis and her saturation was 85%. The cardiovascular examination was unremarkable

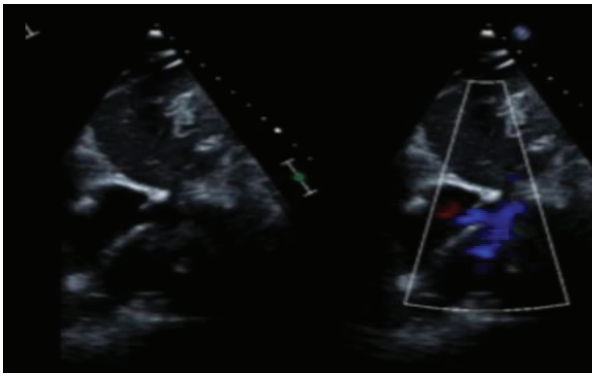


Image 1: There was nothing remarkable on the apical view of transthoracic echocardiography, but a subcostal bi-caval view was suggestive of IVC flow being directed into the left atrium

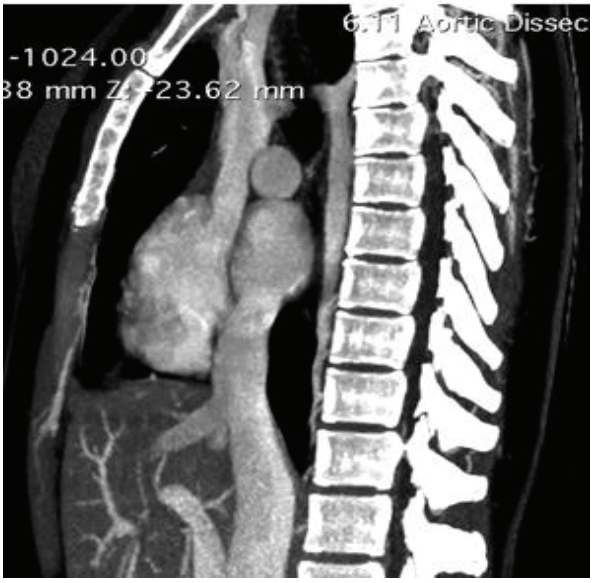


Image 2: Computed tomography with contrast confirmed the same She underwent a corrective re-do surgery with complete relief of her symptoms.

Discussion:

Iatrogenic diversion of IVC blood into the left atrium is a rare complication after ASD surgical closure. It usually occurs due to the incorporation of a prominent Eustachian valve of the IVC into the repair (2-7). It commonly happens with IVC type of defects or rarely with inferiorly located defects with a deficient IVC margin. Another contributing cause is restrained visual access due to a limited incision surgery for cosmetic appearance. Transcatheter closure is usually not associated with such a complication.

Diagnosis of the condition can be made easily by a proper physical examination followed by systematic echocardiographic analysis. Transesophageal echo, Contrast Echo and other advanced imaging like contrast-enhanced CT and MRI can also help aid the diagnosis.

1. van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011; 58:2241.
2. Schwedler G, Lindinger A, Lange PE, et al. Frequency and spectrum of congenital heart defects among live births in Germany: a study of the Competence Network for Congenital Heart Defects. Clin Res Cardiol 2011; 100:1111.
3. Thompson, E., Moritz, D., Perdue, R., & Cansino, S. (2004). Diversion of the inferior vena cava following repair of an atrial septal defect causing hypoxemia. Echocardiography, 21(4), 329-332.
4. Bedford DE, Sellors TH, Somerville W, Belcher JR, Besterman EM. Atrial septal defect and its surgical treatment. Lancet 1957;272:1255-61.
5. Mustard WT. Diversion of the venae cavae into the left atrium during the closure of atrial septal defects. J Thorac Cardiovasc Surg 1964;47:317-24.
6. Shuntoh K, Wada Y, Kawai T, Oka T. Diversion of the inferior vena cava into the left atrium after repair of atrial septal defect with partial anomalous pulmonary venous drainage. Kyobu Geka 1997;50:740-2.
7. Desnick SJ, Neal WA, Nicoloff DM, Moller JH. Residual right-to-left shunt following repair of the atrial septal defect. Ann Thorac Surg 1976;21:291-5.

Dr.Anand Manjunath K*
Dr.G.Ashok**
Dr.M.Chokkalingam***
Department of Cardiology
Chettinad Hospital and research institute, Chennai
Correspondence: dr.g.ashok@gmail.com

Original Article:

ASSESSMENT OF LEFT VENTRICULAR GLOBAL LONGITUINAL STRAIN IN METABOLIC SYNDROME

Abstract

Aims and objectives

To assess the global longitudinal peak systolic strain in patients with metabolic syndrome and the correlation between metabolic syndrome with impaired myocardial function.

Methods:

The study was conducted at the Department of Cardiology, Chettinad Hospital and Research Institute, Chennai. The study population included 200 asymptomatic Metabolic Syndrome patients presenting to the Out-Patient Department. Echocardiographic evaluation of global LV longitudinal strain was done in those with LV ejection fraction (LVEF) ≥ 50% and the correlation of myocardial strain and Metabolic Syndrome and was done.

Results:

The mean age of the study participants was 53.4±11.3 years, 38.5% were in the age group 46-60 years. The majority of the study participants were females (54%).

Raised FBS levels were noted in 84.5%, systemic hypertension in 57.5%, raised triglyceride in 46.5%, and low HDL levels in 53% Nearly 18% and 36% were smokers and alcoholics respectively. No significant association was observed between LV dysfunction by GLS and age, gender, systemic hypertension, raised triglycerides, low HDL levels, Obesity, smoking, and alcoholism status. The proportion of patients with LV dysfunction by GLS was significantly high among patients with diabetes mellitus and higher HBA1C levels.

Conclusions

EF by global longitudinal strain assessed by Speckle Tracking Echocardiography could be used to identify subclinical LV Dysfunction prevalent in patients with Metabolic syndrome who have abnormal FBS or HBA1C levels.

Introduction :

Obesity, mainly abdominal obesity is associated with insulin resistance, which often leads to type 2 diabetes mellitus.1 Hyperinsulinemia, hyperglycemia, adipokines (adipocyte cytokines), abnormal lipid profile, hypertension, and vascular inflammation cause vascular endothelial dysfunction leading to the development of cardiovascular diseases (CVD). The same can be seen in people with just abdominal obesity without an increase in total body weight.2

Metabolic syndrome (MS) carries an increased risk for cardiovascular events.3 Incidence of MS continues to increase over time, compromising the health of the people.4

Subclinical cardiovascular disease is prevalent in patients with Metabolic syndrome. Left ventricular global longitudinal strain assessed by Speckle Tracking Echocardiography (STE) is an index of systolic function: shortening is indicated by negative strain, the better the LV systolic function.

The purpose of this study was to evaluate the use of STE to assess myocardial strain as a marker of LV systolic function in an asymptomatic population of patients with Metabolic syndrome and LV ejection fraction (LVEF) ≥ 50%.

Materials and Methods

The study was conducted at the Department of Cardiology, Chettinad Hospital and Research Institute, Chennai. The study population included 200 asymptomatic Metabolic Syndrome patients presenting to the Out-Patient Department. The study period was from January 2017 to December 2018.

The patients having at least three of the following criteria were considered as having metabolic syndrome

1) Fasting Plasma Glucose >100 mg%.
2) Triglycerides >150 mg%.
3) HDL-Cholesterol
   <40mg% in males
   <50mg% in females.
4) Blood Pressure >130/85 mm Hg.
5) Waist circumference
   >102 cm in males
   >88 cm in females.

Adults of age between 35 -70yrs diagnosed with metabolic syndrome as explained above were included in the study after obtaining informed consent. Echocardiography was done and a global LV longitudinal strain was assessed. The data collected were subjected to statistical analysis to look for correlation of myocardial strain in an asymptomatic population and LV ejection fraction (LVEF) ≥ 50%.

Inclusion Criteria:

- Patients with metabolic syndrome
- In the age group of 35 to 70 years

Exclusion Criteria:

- Patients with pre-existing cardiomyopathy
- Patients with moderate or severe valvular heart disease
- Patients with poor echogenic window
- Patients with CKD

All patients included in the study were worked up as follows:

- A detailed clinical history.
- Thorough physical examination.
- Standard 12 lead ECG
- Blood – CBC, RFT, S. Electrolytes, FBS, PPBS, RBS, FLP
- 2D Echocardiography
- Strain Echo with Esaote my lab 30 CV – ECHO Machine

Statistical Analysis

All data were entered in Excel 2013 and analyzed using SPSS version 22.0. Means and proportions were calculated for continuous and categorical data respectively. Differences in proportions were tested using the chi-square test. Correlation between two continuous variables was tested using the Pearson correlation coefficient. A p-value < 0.05 was considered statistically significant.

Results:

The mean age of the study participants was 53.4±11.3 years, 38.5% were in the age group 46-60 years. The majority of the study participants were females (54%). The majority of the study participants have raised FBS levels (84.5%). 57.5% were Hypertensive,46.5% had elevated Triglyceride levels, and HDL levels <40mg% was noted among 53% of the study participants. The majority of the study participants were found to have raised waist circumference (77.5%).49% of the study participants were overweight and 28.5% obese. A large number of the study participants had their HbA1C levels ranging from 7-10 (49.5%). The majority of the study participants had normal ejection fraction levels by GLS. 31.5% had Metabolic syndrome s defined by the combination of FBS>100mg%, higher Abdominal Circumference, and Systemic hypertension, followed by 27% with a combination of FBS >100mg%, Decreased HDL and higher Abdominal Circumference.

Table 1. Distribution of study participants based on the presence of comorbidities (n=200)

Abnormalities coexisting	**Frequency**	**Percent**
↑FBS , ↑Triglycerides ,↓HDL , ↑Abdominal circumference , **Systemic Hypertension**	9	4.5
↑FBS , ↑Triglycerides ,↑HDL , **Systemic Hypertension**	9	4.5
↑FBS , ↑HDL , ↑Abdominal circumference , **Systemic Hypertension**	16	8.0
↑Triglycerides , ↑HDL , ↑Abdominal **circumference, Systemic Hypertension**	11	5.5
↑FBS , ↑Triglycerides , ↑HDL , ↑Abdominal circumference	13	6.5
↑FBS , ↑Abdominal circumference , **Systemic Hypertension**	63	31.5
↑HDL , ↑Abdominal circumference , **Systemic Hypertension**	24	12.0
↑FBS , ↑HDL , ↑Abdominal **circumference**	54	27.0
↑Triglycerides , ↑HDL ↑Abdominal circumference	18	9.0
↑FBS , ↑Triglycerides ↑Abdominal circumference	51	25.5
↑Triglycerides , ↑Abdominal circumference **Systemic Hypertension**	35	17.5

Distribution of study participants based on GLS Ejection fraction (n=200)		
GLS ejection fraction	**Frequency**	**Percent**
Normal	160	80.0
Mild LV dysfunction	37	18.5
Moderate LV dysfunction	3	1.5
Total	200	100.0

No significant association was observed between age and LV dysfunction (p-value .941) nor between gender and LV dysfunction (p-value -0.710). A higher proportion of patients with FBS>100mg% had LV dysfunction as compared to those with normal FBS(p-value – 0.012). No significant association was observed between the presence of hypertension and LV dysfunction (p-value -0.730). No significant association was observed between raised triglycerides and LV dysfunction (p-value -0.611) nor between lower HDL levels and LV dysfunction (p-value- 0.558). No significant association was observed between the higher abdominal circumference and LV dysfunction (p-value -0.897). Those with higher HbA1C levels were found to have LV dysfunction as compared to those with normal values. (p-value – 0.007).

Table 1. FBS >100mg% and GLS (n = 200)

FBS >100	GLS			Total n (%)	p-value*
	Normal n(%)	Mild LV Dysfunction n (%)	Moderate LV Dysfunction n (%)		
Present	130(76.9)	37(21.9)	2(1.2)	169(100.0)	0.012
Absent	30(96.8)	0(0.0)	1(3.2)	31(100.0)	
Total	160(80.0)	37(18.5)	3(1.5)	200(100.0)	

Systemic Hypertension	GLS and Hypertension			Total n (%)	p-value*
	Normal n(%)	Mild LV Dysfunction n (%)	Moderate LV Dysfunction n (%)		
Present	94(81.7)	18(15.7)	3(2.6)	115(100.0)	0.730
Absent	66(77.6)	19(22.4)	0(0.0)	85(100.0)	
Total	160(80.0)	37(18.5)	3(1.5)	200(100.0)	

Raised triglycerides	GLS and triglyceride level			Total n (%)	p-value*
	Normal n(%)	Mild LV Dysfunction n (%)	Moderate LV Dysfunction n (%)		
Present	72(77.4)	19(20.4)	2(2.2)	93(100.0)	0.611
Absent	88(82.2)	18(16.8)	1(0.9)	107(100.0)	
Total	160(80.0)	37(18.5)	3(1.5)	200(100.0)	

Low HDL levels and GLS (n = 200)					
HDL levels	GLS			Total n (%)	p-value*
	Normal n(%)	Mild LV Dysfunction n (%)	Moderate LV Dysfunction n (%)		
<40	83(78.3)	22(20.8)	1(0.9)	106(100.0)	0.558
>40	77(81.9)	15(16.0)	2(2.1)	94(100.0)	
Total	160(80.0)	37(18.5)	3(1.5)	200(100.0)	

Higher abdominal circumference	Abdominal circumference and GLS			Total n (%)	p-value*
	Normal n(%)	Mild LV Dysfunction n (%)	Moderate LV Dysfunction n (%)		
Present	124(80.0)	29(18.7)	2(1.3)	155(100.0)	0.897
Absent	36(80.0)	8(17.8)	1(2.2)	45(100.0)	
Total	160(80.0)	37(18.5)	3(1.5)	200(100.0)	

Nearly 18% and 36% were smokers and alcoholics respectively. There was no correlation between GLS and Metabolic Syndrome as defined by different combinations.

Abnormalities coexisting	GLS			**p-value**
	Normal n(%)	Mild LV Dysfunction n(%)	Moderate LV Dysfunction n (%)	
↑FBS , ↑Triglycerides ↓HDL , ↑Abdominal **circumference, Systemic Hypertension**	6(66.7)	3(33.3)	0(0.0)	0.479
↑FBS , ↑Triglycerides ↓HDL , **Systemic Hypertension**	6(66.7)	3(33.3)	0(0.0)	0.479
↑FBS , ↓HDL ↑Abdominal circumference **Systemic Hypertension**	11(68.8)	5(31.3)	0(0.0)	0.356
↑Triglycerides , ↓HDL ↑Abdominal circumference **Systemic Hypertension**	8(72.7)	3(27.3)	0(0.0)	0.692
↑FBS , ↑Triglycerides ↓HDL , ↑Abdominal **circumference**	8(61.5)	5(38.5)	0(0.0)	0.150
↑FBS , ↑Abdominal **circumference Systemic Hypertension**	48(76.2)	14(22.2)	1(1.6)	0.650
↓HDL , ↑Abdominal **circumference Systemic Hypertension**	19(79.2)	5(20.8)	0(0.0)	0.782
↑FBS , ↓HDL ,□Abdominal **circumference**	40(74.1)	14(25.9)	0(0.0)	0.162

↑Triglycerides , ↓HDL ↑Abdominal **circumference**	13(72.2)	5(27.8)	0(0.0)	0.505
↑FBS , ↑Triglycerides ↑Abdominal circumference	35(68.6)	15(29.4)	1(2.0)	0.061
↑Triglycerides , ↑Abdominal **circumference** **Systemic Hypertension**	26(74.3)	7(20.0)	2(5.7)	0.073

Association between the presence of HbA1C levels and GLS (n = 200)					
HbA1C levels	GLS			Total n (%)	p-value*
	Normal n(%)	Mild LV Dysfunction n (%)	Moderate LV Dysfunction n (%)		
<6	74(92.5)	5(6.3)	1(1.3)	80(100.0)	0.007
7 to 10	70(70.7)	27(27.3)	2(2.0)	99(100.0)	
>10	16(76.2)	5(23.8)	0(0.0)	98(100.0)	
Total	160(80.0)	37(18.5)	3(1.5)	200(100.0)	

* Chi-Square test was applied to test the statistical difference in proportions

A higher proportion of patients with increased HbA1C levels were found to have LV dysfunction as compared to those with normal levels. Also, this association was found to be statistically significant (p-value – 0.007)

Discussion

The present study was carried out with an objective to assess the global longitudinal peak systolic strain in patients with metabolic syndrome and normal Ejection Fraction and to see if any correlation between metabolic syndrome and impaired myocardial function. Hassan HM et al studied early Left Ventricular diastolic dysfunction in patients with metabolic syndrome by 2D speckle tracking echocardiography based on global longitudinal isovolumic relaxation strain rate among 100 subjects. There were no statistically significant differences between MS and controls in all traditional parameters of LV systolic function. On the other hand, significant differences were observed between MS and the control group in most of the parameters of GLS and SR IVR. A similar observation was noted in the present study.5

Carrubba SL et al evaluated the association between MS and LV dysfunction among 6422 consecutive asymptomatic patients. In the group of patients without MS (n = 5630), the prevalence of systolic dysfunction was 10.8% (n = 607) while in the group of patients with MS (n = 545) it was 12.5% (n = 87), (RR1.57; CI 95% 1.2-2.0; P < 0.001). After adjustment for age and gender, MS proved to be an independent predictor of LV systolic and diastolic dysfunction.6 The present study also showed similar observations in relation to metabolic syndrome and LV dysfunction. The prevalence of systolic dysfunction observed in the above discussed is lower than that of the results of the present study (20.0%). It is also to be noted that LV dysfunction in study patients with MS are subclinical, not detected by routine echocardiography.7

Azevedo A et all evaluated whether a graded association between an increasing number of components of the metabolic syndrome and cardiac structural and functional abnormalities exists among 684 participants. The study results reported that there was a positive association between the number of features of metabolic syndrome and parameters of cardiac structure and function, with a consistent and statistically significant trend for all cardiac variables considered after adjusting for age and gender. Parameters

of left ventricular geometry patterns and diastolic dysfunction maintained this trend when taking into account the 10-year predicted risk of coronary heart disease by the Framingham score as an independent variable, while left ventricular systolic dysfunction did not. The prevalence of left ventricular diastolic dysfunction and the mean left ventricular mass, left ventricular diameter, and left atrial diameter increased significantly with the number of features of the metabolic syndrome. On subgroup analysis only raised FBS and HbA1c was found to be significantly associated with LV dysfunction in the present study, however, none of the other components of its combinations were found to be associated with LV dysfunction among patients with MS.8

CONCLUSION

EF by global longitudinal strain assessed by Speckle Tracking Echocardiography could be used to identify subclinical LV dysfunction prevalent in patients with Metabolic syndrome, particularly in those who have abnormal FBS or HBA1C levels.

REFERENCES:

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
2. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173-94.
3. Lindsay RS, Howard BV. Cardiovascular risk associated with metabolic syndrome. Current diabetes reports 2004;4:63-8.
4. Conus F, Allison DB, Rabasa-Lhoret R, St-Onge M, St-Pierre DH, Tremblay-Lebeau A, et al. Metabolic and behavioral characteristics of metabolically obese but normal-weight women. The Journal of clinical endocrinology and metabolism 2004;89:5013-20
5. Hassan MH, El-Gammal MS, Ahmed A-H, Ali EM. Assessment of Early Left Ventricular Diastolic Dysfunction in Patients with Metabolic Syndrome by 2D Speckle Tracking Echocardiography. The Egyptian Journal of Hospital Medicine 2018;72:4134-43.
6. La Carrubba S, Todaro MC, Zito C, Antonini-Canterin F, Monte IP, Caso P, et al. Asymptomatic Left Ventricular Dysfunction and Metabolic Syndrome: Results from an Italian Multicenter Study. Journal of cardiovascular echography 2013;23:96-101.
7. La Carrubba S, Antonini-Canterin F, Fabiani I, Colonna P, Pugliese NR, Caso P, et al. Prevalence and prognostic impact of metabolic syndrome in asymptomatic (stage A and B heart failure) Patients. Metabolic syndrome and related disorders 2016;14:187-94.
8. Azevedo A, Bettencourt P, Almeida PB, Santos AC, Abreu-Lima C, Hense H-W, et al. Increasing number of components of the metabolic syndrome and cardiac structural and functional abnormalities-the cross-sectional study of the general population. BMC cardiovascular disorders 2007;7:17-19

Dr. Sajan Narayanan. MD. DM.
Little Flower Hospital and
Research Centre, Angamaly.
Correspondence: sajannarayanan@gmail.com

Personal Perspective.

FRACTIONAL FLOW RESERVE IN CLINICAL PRACTICE-STILL RELEVANT IN POST ISCHAEMIA PERIOD?

Introduction

International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) has been presented at AHA 2019 and subsequently published in NEJM on march 30 20201. Patients with at least moderate ischemia on noninvasive evaluation were randomised to invasive versus conservative strategy. Over a follow up period of median 3.2 years, there was no difference in primary endpoints between two treatment arms .

Fractional Flow reserve (FFR) – physiological assessment of functional significance of a coronary lesion has been shown to predict adverse outcomes. An FFR cutoff of <0.75 correlates with ischemia detected on at least 1 noninvasive test to detect ischemia2. An FFR value of >0.75 identifies a lesion which can be managed medically with excellent short term outcome3 with sustained benefit observed at 15 years in DEFER trial4. Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial showed that FFR guided PCI improves outcomes when compared to an angiographic guided strategy in patients scheduled to undergo revascularisation.5 Subsequently FAME 2 trial showed that an FFR value of <0.8 identified stable lesions which could benefit from targeted intervention as opposed to optimal medical treatment6.

With ISCHEMIA generating tremendous interest, casting a genuine scepticism among physicians, cardiologists and patient population alike, about added benefit of an initial invasive strategy in addition to optimal medical treatment in patients with stable ischemic heart disease (SIHD), role of FFR and relevance of earlier landmark trials which showed its utility in SIHD has come under cloud. Present short review aims to find out what is the place for FFR evaluation of stable coronary lesions after publication of ISCHEMIA trial

Since ISCHEMIA specifically included stable angina, this paper intend to focus on FAME 2 as a representative trial of FFR which had randomised similar subset of patients and had an optimal medical treatment arm for comparison

Design of ISCHEMIA & FAME trials

Randomisation of patients in ISCHEMIA trial were exclusively based on noninvasive stress test showing at least moderate ischemia in stress imaging (nuclear study, stress echo or stress cardiac magnetic resonance) or exercise stress test7. Patients who had atleast moderate ischemia underwent CT coronary angiogram – primarily to rule out left main disease (exclusion criteria for the study). Hence randomisation was performed before invasive angiogram.This was specifically done to exclude selection bias .

In FAME 2, patients with SIHD were subjected to invasive angiogram before randomisation. FFR was performed & lesions with FFR <0.8 were randomised to either percutaneous intervention (PCI) + optimal medical treatment or optimal medical treatment (OMT) alone. Hence FFR was performed in all suspicious lesions detected on invasive angiogram

In ISCHEMIA trial,
FFR was mandatory as per protocol :

A) When cath showed <50% lesion in a patient with moderate ischemia (stress imaging) pertaining to corresponding vascular territory

B) When cath showed lesion in a territory different from that visualised in stress imaging, FFR was mandatory if lesion severity was <80% & to consider if lesion was >80%

C) In patients who underwent exercise stress ECG as entry test and who had <80% lesion on cath.

D) FFR was encouraged when cath showed >80% lesion in patients who had exercise stress ECG as entry test.

Accordingly FFR was performed in 481/2372 (20.3%) of patients who were randomised to invasive strategy8.

Hence in ISCHEMIA, lesion specific ischemia was not assessed, but total ischemic burden was guide to randomisation. Trials which tested utility of FFR (DEFER, FAME, FAME 2), lesion specific ischemic burden was the guide to enrolment.

Comparison of Baseline characteristics :

A comparison of baseline characteristics between ISCHEMIA & FAME 2 trials is shown in the table 1. ISCHEMIA trial had more patients with diabetes & multivessel disease9

	ISCHEMIA	FAME 2
No. of patients randomised	5179	1220
Age	64	63.5 ±9.35
Females	1168/5179 (22.6%)	91/447 (20.4%)
Hypertension	3789/5161 (73.4%)	347/447 (77.6%)
Diabetes	2122/5179 (41%)	123/447 (27.5%)
Prior MI	990/5161(19.2%)	164/442(37.1%)
Multivessel disease (≥50% stenosis)	2679/3390 (79%)	196/447 (43.8%)
Left anterior descending	3190/3677 (86.8%)	279/447 (62.4%)

Table 1: A comparison of baseline characteristics between ISCHEMIA & FAME 2

Comparing burden of ischemia between two trials, 4399/5167 (85%) patients in ISCHEMIA had moderate or severe ischemia. Mean FFR of lesions randomised in FAME 2 was 0.68 + 0.1 indicating atleast moderate ischemia in FAME 2.

ISCHEMIA

Degree of ischemia	
Stress Imaging :	3909/5179(75.5%)
Severe	1748/3901 (44.8%)
Moderate	1600/3901(41%)
Mild	317/3901(8.1%)
None	226/3901(0.3%)
Exercise stress test:	1270/5179(24.5%)
Severe	1051/1266(83%)
Moderate	101/1266(8%)
Mild	34/1266(2.7%)
None	28/1266(2.2%)

FAME 2

Mean no. of lesions <0.8 / patient	1.52 ±0.78
Lesions with FFR <0.8	679/890(76.3%)
Mean FFR in lesions with FFR <0.8	0.68 ± 0.1

Analysis of endpoints

Primary endpoint in ISCHEMIA was a composite of death from cardiovascular causes, Myocardial infarction (MI), hospitalisation for unstable angina, heart failure or resuscitated cardiac arrest. Major secondary endpoints were composite of cardiovascular death or nonfatal MI , Angina and quality of life as assessed by the Seattle Angina Questionnaire (SAQ) - angina frequency and Quality of life (QoL) scales

In FAME 2 trial, Primary endpoint was a composite of death from any cause, nonfatal MI or unplanned hospitalisation leading to urgent revascularisation. Secondary endpoints included cardiac death, nonurgent revascularisation & angina class.

Death

In ISCHEMIA, 5 year cumulative event rate for death was 5.2% (invasive strategy) versus 6.5% (conservative) (estimated difference -1.3% (-3.1% to 0.6%)

In FAME 2 at 5 years , death from cardiac causes was 2.5% (PCI + OMT) versus (v) 1.6 (OMT) with HR 1.54 (0.6 – 3.98).

Hence with regard to hard endpoint of cardiac death, both ISCHEMIA & FAME 2 failed to show a benefit of invasive strategy as opposed to a conservative approach.

Myocardial Infarction:

In ISCHEMIA trial, non procedural MI was defined by 3rd universal definition. Procedural MI were classified using CKMB preferentially for primary definition & Cardiac troponin for secondary definition and more stringent ECG and angiographic criteria than 3rd universal definition.

Procedural MI was higher in invasive strategy – which was 2.6% versus (v) 0.3% at 6 months while at 5 years cumulative event rate was 2.8% v 1.1% (using primary definition). Procedural MI rates were 7.7% v 0.6% at 6 months & 8.4% v 2.0% at 5 year cumulative event rate analysis(using secondary definition). Difference in incidence of procedural MI was more when defined by secondary definition in invasive strategy.

Analysing nonprocedural MI , 6 month cumulative event rate was 1.8% v 2.3% (primary definition) & 1.9% v 2.4% (secondary definition) .

At 5 years analysing all MI (procedural +nonprocedural) difference was 7.1% v 10.0% (primary definition) & 7.3% v 10.2% (secondary definition) . So increase in nonprocedural MI seen with conservative strategy was balanced by higher incidence of procedural MI in invasive strategy .

Incidence of spontaneous MI was significantly reduced by invasive strategy regardless of MI definition.

In FAME 2, which used 3rd universal definition of MI, landmark analysis at 7 days showed higher MI rates in PCI arm with HR 7.99(0.99- 64.6). while beyond 8 days after randomisation, incidence of myocardial infarction was lower in PCI arm with curves diverging further beyond at 3 months and difference persisted at 2 years.At 5 years incidence of MI was 8.1% in PCI arm versus 12.0% in OMT arm which was not statistically significant since 51% of patients in OMT arm underwent revascularisation

Procedural MI were higher in PCI arm in both trials while difference was more when secondary definition was used in ISCHEMIA trial. Both trials showed sustained reduction in incidence of spontaneous MI upto 5 years. Benefit of Invasive strategy appeared as early as 8 days after randomisation in FAME 2 trial while difference emerged after 2 years in ISCHEMIA trial.

Analysis of prognostic impact of MI in ISCHEMIA trial which was presented in ACC 2020 showed that only nonprocedural MI & Type 1 MI according to primary definition predicted all cause death & cardiovascular (CV) death. Procedural MI according to primary or secondary definitions were not predictive of all cause death or CV death10.

Hospitalisation for unstable angina / urgent revascularisation

In ISCHEMIA trial, an important primary endpoint was hospitalisation for unstable angina. In FAME 2 corresponding endpoint is the need for urgent revascularisation. Both endpoints need to be analysed closely.

In ISCHEMIA, hospitalisation for unstable angina was lower in invasive arm – 5 year cumulative event rates being 0.8% v 1.6% with difference started to emerge at 1 year (0.5% v 0.6% (Estimated difference :-0.1% -{0.5% -0.3%})

In FAME 2 need for urgent revascularisation was a primary endpoint which showed significant benefit favouring invasive strategy (1.6% v 11.1%). Urgent revascularisation was triggered by MI in 21.4% , unstable angina accompanied by ECG changes in 26.8% & unstable angina diagnosed on the basis of clinical features in 51.8%. As compared with patients in the medical therapy group, patients in PCI group were significantly less likely to undergo any revascularisation (HR 0.14 95% CI 0.08 – 0.26).

If we analyse effect of invasive versus conservative strategy in prevention of spontaneous events – MI & Unstable angina (Urgent revascularisation was most commonly triggered by unstable angina) both trials have shown that invasive strategy prevents nonprocedural events as compared to conservative strategy.

Angina & Quality of Life:

In ISCHEMIA trial, Median seattle angina questionnaire was 80 – indicating relatively less symptomatic subjects. Only 116/5108 (2.3%) patients reported daily angina while 19.5% had angina on weekly basis & 43.9% had monthly angina. 1756/5108(34.4%) reported no angina in prior 4 weeks of enrolment11.

Among patients who had angina in 4 weeks prior to enrolment, 26.7% had CCS class I , 48.8% had CCS class II & 4.4% had CCS class III angina. 20.1% had no angina in prior 1 month.

In FAME 2 trial, 18.3% had CCS class I, 45.6% class II angina & 17.9% with class III angina .

Proportion of patients with class II & class III combined (life style limiting angina) was 53.2% in ISCHEMIA & 63.5% in FAME 2.

In FAME 2 study, mean FFR in either group was 0.68 + 0.1. Takeshi et al examined correlation between FFR tertiles and QoL among patients enrolled in both FAME & FAME 2. They were divided into upper (0.8 -0.7) , middle (0.69 – 0.51) & lowest (<0.5). Investigators reported there were higher proportion of patients with CCS angina >2 in lower 2 tertiles of FFR12. Hence more symptomatic patients have lower FFR values.

ISCHEMIA study showed that SAQ summary scores improved with invasive strategy in all angina subgroups except in those who didn't have chest pain at baseline. Differences were larger for patients with daily or weekly angina (SAQ improvement by 8.5 points at 3 months & 5.3 points at 36 months).Probablity of being angina free was more in those who had severe symptom

at baseline. In patients who had weekly angina, 45% of those who were in invasive arm were expected to be free of symptom at 3 months compared to 15% in conservative arm.

In patient level pooled analysis of FAME & FAME 2 trials, EQ -5D index improvement was noted in all subgroups with abnormal FFR. Patients who were in lowest tertile of FFR had greatest improvement. Those who achieved larger change in FFR after intervention (delta FFR) had greater improvement in symptoms assessed by EQ-5D index at 1 month & 1 year.

It is apparent that more symptomatic patients benefit from invasive strategy in ISCHEMIA trial and there is a graded effect of treatment based on baseline symptom status. In FAME trials, lower FFR correlated with worse functional class and they derived better symptomatic benefit from invasive strategy.

Can ISCHEMIA algorithm be modified?

ISCHEMIA study used CTCA to detect coronary lesions. Assessment of fractional flow reserve is an invasive procedure, needs hyperemic agent which can be associated with minor side effects. Adding FFRCT to CTCA assessment can improve identification of patients who could benefit from invasive strategy. PLATFORM study found that CTCA + FFRCT can provide more cost effective triage for invasive procedures as compared to usual strategies13. A substudy of PROMISE trial which examined the benefit of FFRCT among patients with stable angina who were refered for invasive angiogram after CTCA, found that a FFRCT of <0.8 predicted need for revascularisation or MACE than decision based on severity of stenosis by CTCA alone14. There was significant disagreement between anatomical assessment of severity by CTCA (31%) and invasive angiogram (29%) with functional assessment by FFRCT14. This data matches with analysis from FAME trial which showed disagreement between severity of lesion assessment with angiogram versus FFR in 25% of subjects15. ADVANCED registry showed that in patients with suspected CAD and refered for CTCA, FFRCT of <0.8 identified subjects who had higher cardiovascular death or myocardial infarction at 1 year16. Hence in patients with ISCHEMIA like entry criteria, adding FFRCT to CTCA could identify functionally significant lesions who could benefit from an invasive strategy .

ISCHEMIA & FAME 2 – summary

ISCHEMIA	FAME 2
Non invasive stress test as entry criteria Moderate – severe ischemia	Invasive angiogram with lesions ≥50% FFR ≤0.8
No difference in all cause death /CV death	No difference in death
Procedural MI was more in invasive arm Spontaneous MI was low in invasive arm Difference in incidence of total MI seen >2 years	Procedural MI was more in PCI arm Spontaneous MI was consistently low in PCI arm upto 5 years Difference in incidence of total MI seen > 7 days
Symptom relief & better QoL in invasive strategy Symptom relief correlate with worse baseline angina status	Symptom relief better with PCI Better angina relief with worse baseline FFR

CONCLUDING REMARKS:

- Patients with stable ischemic heart disease, who have moderate – severe ischemia on noninvasive tests, addition of FFR would help to refine patient & lesion selection.
- FFR identifies clinically & prognostically relevant lesion with great spatial resolution.
- Fractional flow reserve predicts functional improvement after invasive treatment.
- In patients with stable ischemic heart disease with moder ate – severe ischemia, Invasive strategy reduces spontaneous acute coronary events.
- Baseline angina class predicts functional improvement after intervention with worse functional class deriving more benefit.
- Symptom relief & better QoL in invasive strategy Symp tom relief correlate with worse baseline angina status.

REFERENCES

1) D.J. Maron, J.S. Hochman, H.R. Reynolds, et al.Initial Invasive or Conservative Strategy for Stable Coronary Disease (ISCHEMIA). N Engl J Med 2020; 382:1395-1407 2) Nico H.J.Pijls , M.D., PH.D., Bernard de Bruyne, M.D., Kathinka Peels, M.D, et al .Measurement of Fractional Flow Reserve To Assess The Functional Severity Of Coronary artery Stenoses. N Engl J Med 1996;334:1703-8

3) G. Jan Willem Bech, MD; Bernard De Bruyne, MD, PhD; Nico H.J. Pijls, MD, PhD. et al. Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis (DEFER). Circulation. 2001;103:2928-2934 4) Frederik M. Zimmermann, Angela Ferrara, Nils P. Johnson. et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. European Heart Journal (2015) 36, 3182–3188 . 5) Pim A.L. Tonino, M.D., Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D. et al. Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention (FAME). N Engl J Med 2009;360:213-24.

6) Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D., Bindu Kalesan, M.P.H.et al. Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease (FAME 2). N Engl J Med 2012;367:991-1001

7) David J. Maron, Judith S. Hochman, Sean M. O'Brien. et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) Trial: Rationale and Design . Am Heart J. 2018 Jul;201:124-135

8) Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. Supplement to N Engl J Med 2020;382:1395-407. 9) Judith S. Hochman, MD; Harmony R. Reynolds, MD; Sripal Bangalore, MD, MHA. et al. Baseline Characteristics and Risk Profiles of Participants in the ISCHEMIA Randomized Clinical Trial . JAMA Cardiol. 2019;4(3):273-286 10) Bernard Chaitman, Karen Alexander, Derek Cyr. et al. Variation In Myocardial Infarction Rates By Type And Definition In The ISCHEMIA Trial. e- abstract .909-14. ACC 2020

11) John A. Spertus, M.D., M.P.H., Philip G. Jones, M.S., David J. Maron, M.D. et al. Health-Status Outcomes with Invasive or Conservative Care in Coronary Disease. N Engl J Med 2020; 382:1408-1419

12) Akeshi Nishi, MD Zsolt Piroth, MD Bernard De Bruyne, MD. et al. Fractional Flow Reserve and Quality-of-Life Improvement After Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease . Circulation. 2018;138:1797–1804

13) Pamela S. Douglas, MD, Bernard De Bruyne, MD, Gianluca Pontone, MD. et al. 1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease (PLATFORM) . JAmCollCardiol 2016;68:435–45

14) Michael T. Lu, MD, Maros Ferencik, MD, PHD, Rhonda S. Roberts, MSPH. et al. Noninvasive FFR Derived From Coronary CT Angiography. JACC Cardiovasc Imaging 2017;10:1350-1358.

15) Pim A. L. Tonino, MD, William F. Fearon, MD, Bernard De Bruyne, MD, PHD. et al. Angiographic Versus Functional Severity of Coronary Artery Stenoses in the FAME Study. J Am Coll Cardiol 2010;55:2816–21

16) Patel MR, Norgaard BL, Fairbairn TA, et al. 1-year impact on medical practice and clinical outcomes of FFRCT: the ADVANCE registry. JACC Cardiovasc Imaging. 2020;13:97-105.

Dr. Hisham Ahammed MD.DM.*
Amrita Institute of Medical Sciences,Kochi
Correspondence: hishama@aims.amrita.edu

Review article

OPTIMAL USE OF PPE DURING A PANDEMIC

Introduction

The SARS-CoV-2 causing COVID-19 has reached pandemic levels since March 2020. In this context, protective measures against SARS-CoV-2 gain significance for health care personnel (HCP) in direct contact with patients suffering from COVID-19 as well as for ambulatory and hospitalized patients without infection. Given finite health care resources in our setting, health care providers need clear guidance on how to prioritize access to care for individual patients as well as providing care for COVID-19 while not neglecting other life-threatening emergencies.

Risk of SARS-CoV-2 Infection in Health Care Providers:

Recent reports have shown that concerning confirmed COVID-19 cases, 41.3% were considered to have acquired the infection from the hospital and 70% of those patients were HCP.1 Health care providers are at substantially increased risk of contracting the virus as clearly shown by Wu et al, whose analysis revealed that 3.8% of infected individuals (44762 infected patients), were health care professionals.2,3This clearly emphasizes that there should be well-delineated protection protocols for the health care worker in high-risk environments such as out-patient clinics, emergency services, intensive care services, and areas attending to invasive diagnostic as well as therapeutic procedures.

Taking into account that there are only a few documents regarding type and level of protection of HCP, this article considered the ESC guidance document, WHO document,5 the American Center for Disease Control and Prevention guidelines on COVID-19,4 the European Centre for Disease Control guidelines on COVID-19;6 but also Chinese data 7and

experiences from European countries with the largest outbreaks of COVID-19. Importantly, the ESC Guidance document aims to suggest a high level of protection for HCP in the worst transmission scenario of SARS-CoV-2 infection. Different settings, such as countries with no cases, countries with sporadic cases, countries experiencing case clusters in time, geographic location and/or common exposure should prepare to respond to different public health scenarios, recognizing that there is no one size fits all approach to managing cases and outbreaks of COVID-19.

Each country should dynamically assess its risk and rapidly change the definitions according to their local situation, depending on the phase of the epidemic, demography, healthcare capacity, and governmental/local health authorities' decisions

Levels of protection for the healthcare worker

The levels of protection that is to be provided for the health care worker is determined by:

1. Patient risk assessment and status (Table 1) 5

2. Procedure performed

In addition to the recommendations of personal protective equipment (PPE) for the health care worker, it is imperative that any patient with suspected or confirmed COVID 19 status, should be wearing a disposable surgical mask in the presence of a health care worker or others in the hospital.

Personal protection management recommendations for SARS-CoV2: 5,8

1. Level 1 protection: The clinical settings which come under level 1 protection would include pre-examination triage and out-patient clinic (patients with no suspicion or low probability of SARS-CoV2).

PPE recommendation for level 1: Disposable surgical cap, Disposable surgical mask, Work uniform, and Latex gloves.

2. **Level 2 protection:** The clinical settings coming under level 2 protection include the following:

a. All suspected or probable/confirmed cases of COVID 19 (patients should wear a disposable surgical mask)

b. Outpatient department (suspected/probable or confirmed cases of COVID 19)

c. Isolation ward and intensive care units

d. Non-respiratory specimen examination of suspected/probable or confirmed COVID 19 patients

e. TEE (Trans-oesophageal echo) in a suspected/probable or confirmed COVID 19 patient

f. Percutaneous invasive procedures such as coronary angiography, PCI, EP studies in suspected/probable or confirmed COVID 19 patients

g. Cleaning of surgical or diagnostic instruments (TEE / TTE transducers, stethoscope) in suspected/probable or confirmed COVID 19 patients

PPE recommendation for level 2: Disposable surgical cap, Medical protection masks (N95, FFP2), Work uniform, Gown, Disposable surgical gloves, and Goggles. (FFP stands for Filtering Face-Piece Respirator Masks). In the situation of a shortage of mask supplies, FFP2 and FFP3 masks can be worn up to 6 hours. An FFP3 mask is preferred for a TEE examination. Personal eyeglasses or contact lenses are not considered appropriate eye protection.

3. **Level 3 protection:** The clinical settings which qualify for level 3 protection include aerosol-generating procedures such as nasopharyngeal swabs, endotracheal intubation, or other procedures in which the suspected/probable or confirmed COVID 19 patient may spray or splash respiratory secretions, blood or body fluids.

PPE recommendation for level 3: Disposable surgical cap, Medical Protection Mask (FFP3), Work uniform, Gown, Disposable surgical gloves, and Goggles. If available, full face respiratory protective devices or powered air-purifying respirators are also recommended.

FFP2, FFP3, and N95 masks are designed to achieve a close facial fit and thus achieve efficient filtration of airborne particles. Powered air-purifying respirator (PAPR) is a form of PPE, in which a respirator in the form of a hood takes ambient air after an active filtration process and delivers the filtered air to the user. Fig 1 illustrates the various types of masks recom-

mended for the various levels of PPE recommendations.

General considerations in the application of PPE recommendations

A. All healthcare workers must be proficient in the proper techniques for donning and doffing PPE. Fig 2 illustrates the recommended sequence for donning and Fig 3 illustrates the same for doffing. 7

B. **Ambulatory setting considerations:** It is strongly recommended that every patient and healthcare worker in the outpatient clinic be given a surgical mask. If the patient risk status is higher, level 2 protection guidelines will need to be instituted. A comprehensive triage system would identify a suspected/probable case or a case with low suspicion. The suspected/probable cases should be managed in a dedicated ambulatory setting with level 2 protection for the HCP. The cases with a low suspicion for COVID 19 can be managed in an ambulatory setting with level 1 protection for the HCP. 4

C. **Ward setting considerations:** Newly admitted patients, especially within the context of community transmission, should be considered as a suspected/probable case of COVID 19. In such instances, while the patient is being evaluated with a swab test, level 2, or level 3 protection must be in place. The use of dedicated medical equipment for these patients is strongly recommended (blood pressure cuffs, thermometers, stethoscopes) along with clear disinfection protocols according to institutional guidelines. If the patient tests negative for COVID 19 (may require more than one test if clinical suspicion is high), then level 1 protection recommendations can be followed thereafter. 3,4,6,9

D. **Emergency department considerations:** COVID 19 triage is of paramount importance in the emergency department. If the consultation in the emergency department is urgent for a suspected/probable COVID 19 patient and a result of a swab test is not available, then the patient should be considered as a confirmed case of COVID 19. This will require level 2 protection recommendations or level 3 if aerosol-generating procedures are being considered. Patients who are considered to be having a low probability for COVID 19 may be managed with level 1 protection measures in the emergency department. 4

E. **Intensive care unit considerations:** Since the patients(suspected/probable or confirmed) admitted to intensive care are likely to be unstable patients who may be on ventilator support or likely to be ventilated, a high level of protection must be given to all healthcare workers in the intensive care unit. Level 2 or Level 3 protection recommendations are strongly recommended.7

F. **Catheterization laboratory considerations:** The cardiac catheterization team must be well versed in the donning and doffing sequence of PPE. All patients entering the catheterization lab must be wearing a surgical mask. 7

STEMI / High-risk NSTEMI: The procedure is to be performed in a dedicated COVID 19 catheterization laboratory and regions with high community level of transmission, it would be prudent to consider every patient as possible COVID 19 patients and HCP protection instituted (Level 2 or Level 3) (Level 3 recommendations when there is a potential for aerosol generation). In regions with the low community-level transmission, patients may be risk-stratified based on Table 1 and appropriate protection measures are chosen. If the intervention is to be performed in a confirmed case of COVID 19, the catheterization team should be minimized and level 2 or level 3 protection recommendations must be followed (Level 3 recommendations when there is a potential for aerosol generation)

Any intubation or CPR in the catheterization lab has a high likelihood of generating aerosols of the respiratory secretions and if available, a powered air-purifying respirator can be considered. In the case of manual ventilation during CPR, a high-efficiency particulate filter may be placed between the bag valve mask and the endotracheal tube.

A terminal cleaning and sanitization after each case should be achieved. The frequency of air exchange in the lab should ideally be 30 exchanges per hour.

G. **Electrophysiology lab considerations:** All patients with an electrophysiology study indication should undergo a risk assessment based on Table 1. Based on the risk assessment status, the respective level of PPE recommendations should be followed. In cases of hemodynamic instability or critical conditions (eg. complete AV block and syncope), the patient must be deemed as COVID 19 positive, and level 2 or level 3 recommendations must be instituted (Level 3 recommendations when there is

a potential for aerosol generation). Such patients will be subsequently monitored at a dedicated facility and be evaluated for COVID 19 with swab tests.

A confirmed COVID 19 patient should prompt the minimization of staff in the lab and institution of level 2 or level 3 PPE recommendations. Cleaning and sanitization should follow after every procedure based on institutional guidelines.

H. **TEE considerations:** The oropharyngeal secretions in a COVID 19 patient has a very high viral load. Therefore, the operator and assistants during a TEE must be meticulous in adhering to the PPE recommendations. All patients scheduled for a TEE must undertake a swab test and if two successive swab tests are negative, the patient may be taken up for the TEE procedure with level 2 or preferably level 3 PPE recommendations. 10

Conclusion

The SARS-CoV2 pandemic has brought into focus the need for dedicated protocols to ensure adequate protection for the healthcare worker and patients. As our understanding of the virus characteristics and transmission dynamics are still in a state of flux, we anticipate that the guidelines elucidated here will see modifications as we move deeper into this pandemic. However, we have understood certain core principles regarding the risk assessment of a patient and in response, modulating our PPE recommendations based on that initial process of risk stratification. These principles will stand us in good stead, not only to deliver optimum protection from the present COVID 19 pandemic, but also in the next raging pandemic lurking on the horizon.

References

1. Luo M, Cao S, Wei L, Tang R, Hong S, Liu R, Wang Y. Precautions for Intubating Patients with COVID-19. Anesthesiology: The Journal of the American Society of Anesthesiologists 2020. https://doi.org/10.1097/aln.0000000000003288
2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020. https://doi.org/10.1001/jama.2020.2648
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020;395(10223):497- 506. https://doi.org/10.1016/S0140-6736(20)30183-5
4. Center for Disease Control and Prevention. Coronavirus (COVID- 19). https://www.cdc.gov/coronavirus/2019-nCoV/index.html
5. World Health Organization. Global surveillance for COVID-19 caused by human infection with COVID-19 virus: interim guidance, 20 March 2020. (2020; date last accessed). https://extranet.who.int/iris/restricted/handle/10665/331506
6. European Centre for Disease Prevention and Control. ECDC technical report- Infection prevention and control for COVID-19 in healthcare settings - first update 12 March 2020 (March 12, 2020; date last accessed). https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-infectionprevention-and-control-healthcare-settings-march-2020.pdf
7. Editor-in-Chief P, Yu L. Handbook of COVID-19 Prevention and Treatment; 2020. https://covid-19.alibabacloud.com/
8. World Health Organization. Advice on the use of masks in the context of COVID- 19. (April 6, 2020; date last accessed). https://www.who.int/publicationsdetail/advice-on-the-use-of-masks-in-the-community-during-home-care-and-inhealth-care-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak
9. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, Fan Y, Zheng C. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet Infectious Diseases 2020;20(4):425-434. https://doi.org/10.1016/S1473- 3099(20)30086-4
10. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia Ja, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet 2020;395(10223):507-513. https://doi.org/10.1016/S0140-6736(20)30211-7

Figure 1

Figure 2 (Donning sequence of PPE)

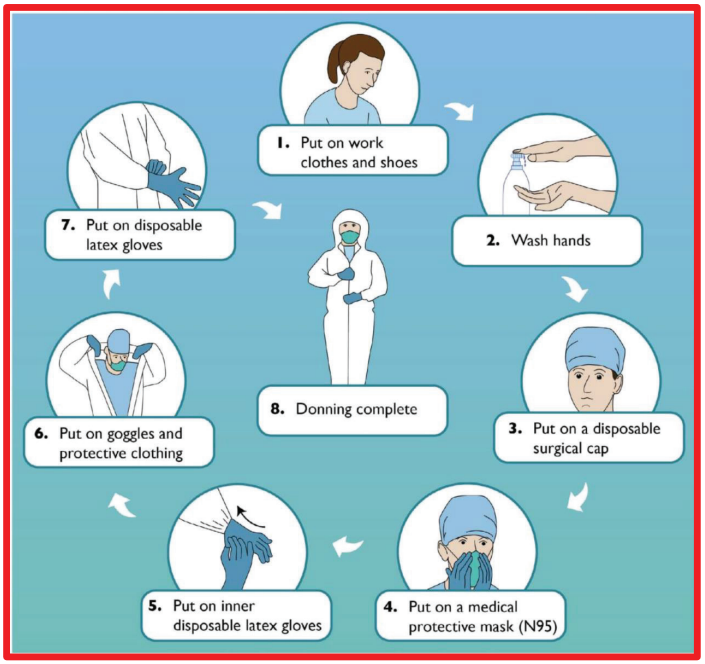
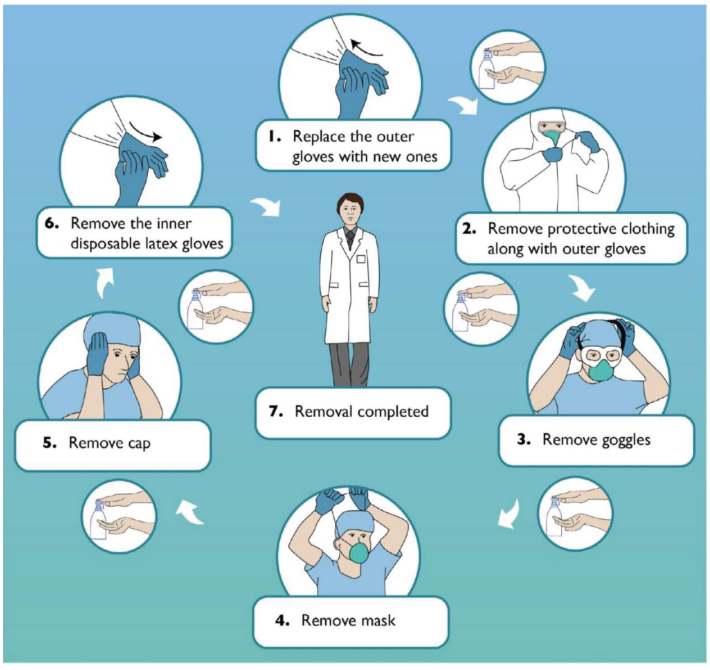


Figure 3 (Doffing sequence of PPE)



Source of Fig 1, Fig 2 and Fig 3 : ESC Guidance for the diagnosis and management of CV disease during the COVID 19 pandemic

(Risk stratification of patient status)

Confirmed Case	Patient with laboratory confirmed SARS -CoV2 infection irrespective of clinical signs or symptoms
Probable Case	A) A suspected case for whom SARS-CoV2 testing was inconclusive OR B) A suspected case for whom testing could not be performed for any reason
Suspected Case	A) A patient with fever or at least one sign/symptom compatible with SARS-CoV2 infection AND a history of travel to or residence in a location reporting community transmission during the 14 days prior to symptom onset OR B) A patient with fever or at least one sign/symptom compatible with SARS-CoV2 infection AND having been in contact with a confirmed or probable COVID 19 case in the last 14 days prior to the onset of symptoms OR C) A patient with acute respiratory disease AND requiring hospitalization AND in the absence of an alternative diagnosis which would explain the clinicalpresentation
Negative Case	A) A person without COVID 19 symptoms who had contacts with a confirmed or probable COVID 19 case who has a negative SARS-CoV2 test OR B) A suspected case with two negative SARS-CoV2 tests OR C) A COVID 19 patient who has recovered with two consecutive negative SARS-CoV2 tests which are 48 hours apart

Proposed Kerala Heart House

Cardiological Society of India - Kerala Chapter
Kerala Heart House, 1st Floor, Mampilly Estate Kundanoor,
Maradu P.O., Kochi - 682304