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Editorial Office
Heart House, Jalan Katalia Raya No. 5, Kota Bambu Utara
West Jakarta, 11430 – Indonesia
Telephone: +62 21 5681149 Fax.: +62 21 5684220
Email: ijc@inaheart.org

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AUTHOR GUIDELINES

Indonesian Journal of Cardiology (IJC) is a peer-reviewed and open-access journal established by Indonesian Heart Association (IHA)/*Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI)* on the year 1979. This journal is published to meet the needs of physicians and other health professionals for scientific articles in the cardiovascular field. All articles (research, case report, review article, and others) should be original and has never been published in any magazine/journal. Prior to publication, every manuscript will be subjected to double-blind review by peer-reviewers. We consider articles on all aspects of the cardiovascular system including clinical, translational, epidemiological, and basic studies.

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3. All tables and figures should be separated from the text. Tables should be submitted in Microsoft Word 97 format and completed with figure legend. Figures should be submitted in TIFF or JPEG format with clear captions.
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Sources of funding

All sources of support for the research should be listed under this heading.

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Original Article

Systolic Blood Pressure, Cardiac Index and Eisenmenger Syndrome are Predictors of Mortality in Pulmonary Arterial Hypertension–associated with Congenital Heart Disease: An Analysis from the COHARD–PH Registry

Muflihatul Baroroh Rochmat,[1] Anggoro Budi Hartopo,[1] Budi Yuli Setianto,[1] Dyah Wulan Anggrahini,[1] Lucia Kris Dinarti.[1]

Abstract
Background: Pulmonary arterial hypertension (PAH) is a complication of left-to-right intracardiac shunt congenital heart disease (LtR-shunt CHD). There are several known predictors of mortality in PAH patients, however, predictors of mortality in LtR-shunt CHD-associated PAH need to be validated.
Objectives: We aimed to investigate the predictors of mortality among adult LtR-shunt CHD-associated PAH patients.
Methods: This retrospective cohort study included adult patients with LtR-shunt CHD-associated PAH retrieved from the COHARD-PH registry. Several baseline variables were selected as potential predictors of mortality, namely (1) clinical data: WHO-functional class, SaO2, 6-min walking distance, systolic blood pressure, and Eisenmenger syndrome; (2) laboratory data: hemoglobin and NT-pro BNP levels; (3) echocardiography data: pericardial effusion, defect size, and TAPSE; and (4) hemodynamic data: right atrial pressure, cardiac output and index, SvO2, and flow ratio. The mortality outcome was assessed from the cohort registry.
Results: A total of 124 subjects with LtR-shunt CHD-associated PAH were included. Sixteen subjects (12.9%) died during the follow-up period. The baseline variables that were significantly associated with mortality were lower systolic blood pressure, Eisenmenger syndrome, higher NT-pro BNP level, and lower cardiac output. The multivariable analysis showed that systolic blood pressure <100 mmHg (OR 10.99; 95% CI 2.54-47.51, p=0.001), cardiac index <2.5 L/min/m^2 (OR 8.13; 95% CI: 1.59-42.28, p=0.011) and Eisenmenger syndrome (OR 3.87; 95% CI: 1.06-14.07) were the independent predictors for mortality.
Conclusions: The systolic blood pressure <100 mmHg, cardiac index <2.5 L/min/m^2, and Eisenmenger syndrome were independent predictors of mortality among adults with LtR-shunt CHD-associated PAH.

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Keywords: *Congenital heart defects; pulmonary hypertension; mortality; Eisenmenger syndrome*.

[1] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia.

Correspondence:
Anggoro Budi Hartopo, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia.
Email: a_bhartopo@ugm.ac.id

Introduction

Pulmonary arterial hypertension (PAH) is an advanced disease with ultimate morbidity as right heart failure and finally leading to cardiac arrest and death. Despite the availability of drugs and improvement in patient management, the data show that the last 3 years of survival rates among patients with PAH are still poor, with an estimate of around 55-75%.[1] Pulmonary arterial hypertension (PAH) is the most common complication faced by congenital heart disease (CHD) patients, especially those with large left-to-right intracardiac shunt (LtR-shunt CHD), which eventually leads to Eisenmenger syndrome.[2] Excessive blood flow, due to left-to-right shunts, through pulmonary circulation leads to endothelial dysfunction, vessel remodeling, raised vascular resistance, and eventually shunts flow reversal.[2] The LtR-shunt CHD-associated PAH consists of four distinctive phenotypes based on current classification all of which convey individual prognostic significance.[2,3]

The prevalence of LtR-shunt CHD-associated PAH in developing countries ranges from 1.6 to 12.5 cases per million adults, with 25-50% of patients with Eisenmenger syndrome.[2,4] The COngenital HeARt Disease in adult and Pulmonary Hypertension (COHARD-PH) registry, the single-center hospital-based registry in Indonesia, found that more than 70% of registered patients with CHD had already developed PAH, who were mostly atrial septal defect (ASD).[5] Prognostic studies for CHD-associated PAH were limited. A current prospective study involving 91 adults (76 % with Eisenmenger syndrome) showed that the higher NT-proBNP level and reduced right ventricle function were independent predictors of mortality.[6] A retrospective study with a larger number of subjects (366 patients) showed that small defects with PAH (3 %) had the worst mortality prognostic, even as compared to Eisenmenger syndrome (26.8%), and found that WHO functional class III-IV, age at diagnosis < 10 years, elevated right atrial pressure > 15 mmHg, and baseline indexed PVR > 8 WU•m^2 were a predictor for mortality.[7] Based on the European Society of Cardiology (ESC) guideline for Pulmonary Hypertension, risk stratification for 1-year mortality has been developed,[3] however its utility in CHD-associated PAH needs evaluation. Since the Indonesian COHARD-PH registry had already collected prospective data, the prognostic study among Indonesians needs to be conducted to corroborate the previously reported data and include the ESC risk stratification model.

In the current study, we investigated the mortality outcome and its predictors among adult patients with LtR-shunt CHD-associated PAH. We retrieved the prospective data of the COHARD-PH registry, a single-center Indonesian registry. This study aimed to assess which predictors significantly predicted mortality among adult patients with LtR-shunt CHD-associated PAH.

Methods

This research was an observational study. The research design was a retrospective cohort study. The data were extracted from the COHARD-PH registry database.[5] The data of adult patients with LtR-shunt CHD-associated PAH were taken from the registry period of July 2012 – October 2020. This research protocol was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada-Dr. Sardjito Hospital, Yogyakarta, Indonesia with the number KE/FK/0381/EC/2021.

Subjects

The study was conducted by collecting data of demography, clinical presentation, laboratory measurement, echocardiographic result, and right heart catheterization (RHC) results at the index of diagnosis as baseline. Patients with LtR-shunt CHD-associated PAH who met the inclusion and exclusion criteria were collected from the COHARD-PH registry. The protocol of the COHARD-PH registry had been published elsewhere.[5]

The inclusion criteria were as follows: 1) patients registered in the COHARD-PH registry with complete baseline data required in this study, 2) patients with simple intracardiac LtR-shunt CHD, namely ASD, ventricle septal defects (VSD) or patent ductus arteriosus (PDA), 3) patients with uncorrected defects at the baseline, and 4) patients with PAH by hemodynamic criteria, namely mean pulmonary artery pressure (mPAP) >20 mmHg, pulmonary vascular resistance (PVR) ≥ 3 Wood unit, and pulmonary artery wedge pressure (PAWP) <15

Table 1. Baseline characteristics of subjects and their comparison between subjects who survived and subjects who died .

Characteristics	All subjects (n=124)	Survived (n=108)	Died (n=16)	P value
Age (years)*	32.5 (18-64)	33 (18-61)	28 (21-64)	0.526
Female sex, n (%)	107 (86.3)	92 (85.2)	15 (93.8)	0.696
Body mass index (kg/m2)*	17.6 (12.2-31.2)	17.7 (12.2-31.2)	16.7 (12.8-21.7)	0.125
Systolic blood pressure (mmHg)*	112.5 (80-179)	117.0 (85-179)	100.0 (80-140)	0.004
Heart rate (beat/min)*	89 (50-152)	89 (50-152)	96 (63-141)	0.602
SaO2 (%)*	95 (63-99)	95 (63-99)	93 (77-99)	0.309
WHO-fc I-II, n (%)	99 (79.8)	86 (79.6)	13 (81.3)	1.000
WHO-fc III-IV, n (%)	25 (20.2)	22 (20.4)	3 (18.8)	1.000
6 min walk distance (m)*	334 (79-580)	338 (79-580)	315 (158-420)	0.117
Haemoglobin (g/dL), mean±SD	14.47±2.27	14.47±2.28	14.49±2.32	0.976
NT-pro-BNP level (pg/mL)*	946.5 (33-35,000)	925 (33-35,000)	2,062 (237-11,674)	0.020
Pericardial effusion, n (%)	3 (2.4)	3 (2.8)	0 (0)	1.000
Defect size ≥2 cm, n (%)	94 (75.8)	80 (74.1)	14 (87.05)	0.353
TAPSE (mm)*	23.0 (9.0-39.0)	23.0 (9.0-39.0)	23.5 (15.0-34.0)	0.905
Left ventricle EF (%), mean±SD	71.19±9.59	71.24±9.75	70.81±8.71	0.868
mean PAP (mmHg), mean±SD	58.94±17.64	58.53±17.57	61.69±18.41	0.506
RA pressure (mmHg)*	8 (1.0-30.0)	9.0 (2.0-30.0)	7.0 (1.0-14.0)	0.602
Cardiac output (L/min)*	3.3 (1.6-100.67)	3.39 (1.60-100.67)	2.86 (1.95-6.10)	0.024
Cardiac index <2 (L/min/m2), n (%)	34 (27.4)	27 (25.0)	7 (43.8)	0.093
SvO2 (%)*	76 (32.0-99.0)	76.8 (32.0-99.0)	70.4 (56.0-90.0)	0.144
Flow ratio ≤1.5, n (%)	52 (41.9)	44.0 (40.7)	8.0 (50.0)	0.484
PAWP (mmHg)*	9.5 (2.0-17.0)	10.0 (2.0-15.0)	9.0 (2.0-17.0)	0.307
PVR (Woods Unit)*	12.5 (3.0-55.0)	11.8 (3.1-55.0)	16.0 (3.0-44.0)	0.188
Atrial septal defect, n (%)	113 (91.1)	98 (90.7)	15 (93.8)	0.660
Ventricle septal defect, n (%)	5 (4.0)	5 (4.6)	0 (0)	0.660
Patent ductus arteriosus, n (%)	6 (4.8)	5 (4.6)	1 (6.3)	0.660
Uncorrected defect, n (%)	112 (90.3)	96 (88.9)	16 (100)	0.362
Bidirectional shunt, n (%)	70 (56.5)	59 (54.6)	11 (68.8)	0.288
Eisenmenger syndrome, n (%)	29 (23.4)	21 (19.4)	8 (50.0)	0.012

*data presented as median (minimum and maximum values)
BP, systolic blood pressure; SaO2, arterial oxygen saturation; WHO-FC, World Health Organization class; TAPSE, tricuspid annular plane systolic excursion; RA, right atrial; SvO2, mixed veins oxygen saturation; EF, ejection fraction; PAP, pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance.

mmHg as measured with RHC at rest.[8] The exclusion criteria were patients who did not have the required follow-up data or could not be contacted to confirm the follow-up or outcome data. Patients with Eisenmenger syndrome at baseline, with the criteria of large septal defects with dominant right-to-left shunts, presence of central cyanosis, secondary polycythemia, and chronic hypoxemia, were also included in this study.

Table 2. The bivariate analysis of variables as predictors of mortality in patients with LtR-shunt CHD-associated PAH.

Variables	Outcomes				p	QR	CI 95%	
	Survived n=108		Died n=16				Min	Max
	n	%	n	%				
Years of age					0.873	0.99	0.95	1.04
Sex					0.369	2.61	0.32	21.15
Females	92	85.2	15	93.7				
Males	16	14.8	1	6.2				
Shunt type								
Pre-tricuspid shunt	98	90.7	15	93.8	1.000	1.53	0.18	12.83
Post-tricuspid shunt	10	9.3	1	6.2				
Corrected defect								
Yes	12	11.1	0	0	0.999	0	0	∞
No	96	88.9	16	100				
Systolic blood pressure								
< 100 mmHg	12	11.1	7	43.7	0.003	6.22	1.96	19.76
≥ 100 mmHg	96	88.9	9	56.3				
WHO-functional class*								
I-II	86	79.6	13	81.3	0.880	0.90	0.24	3.44
III-IV	22	20.4	3	18.7				
6 min walk distance*								
< 165 meters	6	5.6	2	12.5	0.305	2.43	0.45	13.23
≥ 165 meters	102	94.4	14	87.5				
NT-pro BNP level*								
> 1,400 pg/mL	41	37.9	10	62.5	0.063	2.72	0.92	8.05
≤ 1,400 pg/mL	67	62.1	6	37.5				
Pericardial effusion*								
Yes	3	2.8	0	0	0.999	0	0	∞
No	105	97.2	16	100				
TAPSE								
< 18 mm	9	8,3	2	12.5	0,634	1,57	0,31	8,03
≥ 18 mm	99	91.7	14	87.5				
Right atrial pressure*								
≥ 8 mmHg	64	59.3	7	43.8	0.247	0.54	0.18	1.54
< 8 mmHg	44	40.7	9	56.2				
Cardiac index*								
< 2.5 L/min/m2	53	49.1	13	81.3	0.016	4.49	1.21	16.68
≥ 2.5 L/min/m2	55	50.9	3	18.7				
SvO2*								
≤ 65%	17	15.7	4	25.0	0.472	1.78	0.51	6.19
> 65%	91	84.3	12	75.0				
Flow ratio								
≤ 1.5	44	40.7	8	50.0	0.485	1.46	0.51	4.17
> 1.5	64	59.3	8	50.0				
Haemoglobin level								
< 12 g/dL	12	11.1	2	12.5	0.870	1.14	0.23	5.65
≥ 12 g/dL	96	88.9	14	87.5				
Defect size								
< 2 cm	28	25.9	2	12.5	0.255	0.41	0.08	1.91
≥ 2 cm	80	74.1	14	97.5				

SaO2								
< 90%	27	25.0	6	37.5	0.196	1.80	0.59	5.42
≥ 90%	81	75.0	10	62.5				
Eisenmenger syndrome								
Yes	21	19.4	8	50.0	0.007	4.14	1.39	12.32
No	87	80.6	8	50.0				

*variables derived from ESC guideline for risk stratification for prognostic of PAH3, which divided into two categories for this analysis
OR, odd ratio; CI, confidence interval; WHO-FC, World Health Organization class; 6MWD, 6-minute walk distance; TAPSE, tricuspid annular plane systolic excursion; CI, cardiac index; SvO2, mixed vein oxygen saturation; FR, flow ratio; Hb, hemoglobin; SaO2, arterial oxygen saturation.

Data collection and outcome assessment

Data collection was performed by extracting the data from the COHARD-PH registry database. Demography data were sex, age, and body mass index. Clinical data were systolic blood pressure, heart rate, WHO-functional class (WHO-fc), peripheral O2 saturation (SaO2), and 6-minute walking distance. Systolic blood pressure and SaO2 were measured from the upper extremity with a calibrated digital tensimeter and pulse oximeter respectively, during outpatient clinic visits at index of diagnosis (mean value from three measurements in the same visit). A 6-minute walking distance was derived from a 6-minute walking test performed in the hospital's Cardiac Rehabilitation Division by trained nurses. The laboratory data were hemoglobin and NT-pro BNP levels, performed with an automatic hemocytometer (Sysmex, Japan) and electrochemiluminescence immunoassay (Roche Diagnostic, Germany) respectively. The echocardiography data were collected from transthoracic (TTE) and transesophageal (TOE) echocardiography data. The hemodynamic data were collected from the RHC procedure performed in our hospital. All baseline data were collected at the index of PAH diagnosis. The index of PAH diagnosis was defined as a starting point of observation.

The outcome of this study was mortality, which was defined as death from any cause or all-cause mortality during follow-up. Subjects who underwent defect correction during follow-up were still included and analyzed in this study. The data of mortality was retrieved from the registry database. For outcome data completion, the subjects or family members were contacted by telephone or messages to confirm the outcome during the follow-up period (the end of the follow-up was October 2020). Therefore, the length of observation was ranging from 6 months to 105 months (8 years and 9 months).

Statistical analysis

The SPSS v.23 (IBM Corp., Armonk, N.Y., U.S.A) statistics software was used for analysis. The numerical data were assessed by normality test with the Kolmogorov-Smirnov test, and $p > 0.05$ indicated the data were normally distributed. Independent T-tests and Mann Whitney-U tests were applied to analyze the differences between groups among numerical data. A bivariate test with a logistic regression analysis was performed to analyze the association between predictors and mortality. The bivariate association which had a p-value < 0.25 was subsequently included in the multivariable analysis for the multiple logistic regression analysis. The independent association between predictors and mortality was deemed significant if there was a p-value < 0.05 in the multivariable analysis.

Results

Subjects and baseline characteristics

A total of 184 patients with LtR-shunt CHD-associated PAH were recorded in the COHARD-PH registry. As many as 60 patients were excluded. They were excluded due to: the absence of 6 min walking distance data (n=26), the absence of NT-pro BNP data (n=16), the absence of follow-up data (n=10), the absence of both 6 min walking distance data and NT pro-BNP data (n=6), and absence of all 6 min walking

Table 3. The multivariate analysis for predictors of mortality in LtR-shunt CHD-associated PAH.

Predictors	p-value	Adjusted OR	CI 95%	
			Min	Max
Systolic blood pressure <100 mmHg	0.001	10.99	2.54	47.51
NT-pro BNP level >1,400 pg/mL	0.271	2.01	0.58	6.95
Right atrial pressure ≥ 8 mmHg	0.139	0.36	0.09	1.38
Cardiac index < 2.5 L/min/m2	0.013	8.13	1.56	42.28
SaO2 < 90%	0.309	2.06	0.51	8.34
Eisenmenger syndrome	0.040	3.87	1.06	14.07

*OR, odd ratio; CI, confidence interval; SaO2, arterial oxygen saturation

distance, NT-pro BNP data and follow-up data (n=1). Eventually, 124 LtR-shunt CHD-associated PAH subjects were analyzed in this study. Among them, 16 subjects died during follow-up (12.9%). The range of the follow-up period was 6 months to 105 months (8 years 9 months).

The subjects had ages ranging from 18 to 64 years old. There was no age difference between subjects who died and those who survived. Females predominated in the subjects who survived (85.2%) and those who died (93.8%). Based on the type of CHD, subjects who survived consisted of ASD (90.7%), VSD (4.6%), and PDA (4.6%). In subjects who died, the CHD was ASD (93.8%) PDA (6.3%), and no VSD. Eisenmenger syndrome was significantly higher among subjects who died (50.0% vs. 19.4%, p=0.012). Twelve subjects underwent shunt correction during follow-up, and all of them were in the survivor group. The systolic blood pressure was significantly lesser in those who died (median: 117 mmHg vs. 100 mmHg, p=0.04). The level of NT-proBNP was significantly elevated in those who died as compared to survivors (median: 2,062 pg/mL vs. 925 pg/mL, p=0.020). The hemodynamic data showed that cardiac output was significantly lower in subjects who died as compared to those who survived (median: 2.86 L/min vs. 3.39 L/min). There was a trend that more subjects who died had reduced cardiac index <2 L/min/m2 as compared to subjects who survived (43.8% vs. 25.0%, p=0.093). Based on ESC risk stratification, cardiac index <2 L/min/m2 is categorized as high risk. The baseline characteristics of all subjects, and data concerning subjects who survived and died are shown in Table 1.

The analysis for predictors of mortality

For bivariate analysis, several variables derived from the ESC guideline of risk stratification and prognostic factors were converted into two categorical data, namely WHO f.c, 6 min walking distance, NT-pro-BNP level, presence of pericardial effusion, right atrial pressure, cardiac index and SvO2.[3,7] The results of the bivariate analysis for predictors of mortality are shown in Table 2. The systolic blood pressure <100 mmHg (odds ratio: 6.22; 95% CI: 1.96-19.76, p=0.003), cardiac index <2.5 L/min/m2 (odds ratio: 4.49; 95% CI: 1.21-16.68, p=0.016) and Eisenmenger syndrome (odds ratio: 4.14; 95% CI: 1.39-12.32, p=0.007) were the statistically significant predictors associated with mortality. The NT-pro-BNP level >1400 pg/mL (p=0.063), right atrial pressure ≥ 8 mmHg (p=0.247), and SaO2 <90% (p=0.196), along with systolic blood pressure, cardiac index, and Eisenmenger syndrome, were included for further analysis with multivariable logistic regression test.

The multivariable analysis showed that systolic blood pressure <100 mmHg (adjusted odds ratio: 10.99; 95% CI: 2.54-47.51, p=0.001), cardiac index <2.5 l/min/m2 (adjusted odds ratio: 8.13; 95% CI: 1.59-42.28, p=0.011) and the presence of Eisenmenger syndrome (adjusted odds ratio: 3.87; 95% CI: 1.06-14.07, p=0.040) were the independent predictors for mortality (as shown in table 3).

Discussion

The results of this study showed that there were three independent predictors for mortality of adult

patients with left-to-right intracardiac shunt CHD-associated PAH, namely systolic blood pressure <100 mmHg, cardiac index <2.5 L/min/m2 and the presence of Eisenmenger syndrome. The results highlight the importance of these three parameters at the index of diagnosis to be considered as risk modifiers for mortality, therefore the intensification of drug therapy must be emphasized.

In this study, the type of underlying shunt-defect CHD was divided into three simple defects, namely ASD, VSD, and PDA. Most subjects had ASD (pre-tricuspid shunt) followed by PDA and VSD (post-tricuspid shunt). Most subjects who died were ASD, however, this type was also observed in subjects who survived. All subjects who died had uncorrectable defects, based on RHC parameters, while in subjects who survived, 88.9% were uncorrectable defects. Therefore, all subjects who had defect correction (11.1%) survived. Supporting our study, the previous study involving a large number of patients with simple CHD, moderately complex CHD, and severely complex CHD, the mortality rate was higher than average in patients with ASD.[7,9,10]

The bidirectional shunt, detected by TTE and TOE, was more prevalent in subjects who died. Eisenmenger syndrome was an independent predictor of mortality in this study. This agrees with a previous study which showed that among patients with Eisenmenger syndrome, the location of the defect has prognostic implications between pre-tricuspid, post-tricuspid, and complex lesions.[9] It showed that the pre-tricuspid defect, such as ASD, had a lower 5-year survival rate as compared with the post-tricuspid defect and even the complex lesion group.[7] The predictors of mortality in the previous study were: WHO f.c III/IV, age < 10 years old at baseline, PAH with a small defect, right atrial pressure >15 mmHg, and PVR >8 Woods Unit at baseline measurement.[7,10] However, our study found different independent mortality predictors from a previous study in the same region.

The NT-pro-BNP level was significantly higher in subjects who died. Despite its non-statistical significance, the NT-pro-BNP level >1,400 pg/mL had a mortality risk two times greater in our study. Previous study showed that an increase in NT-pro-BNP was a predictor of PAH mortality in a single model and the multivariate model, increased NT-pro BNP remained independently associated with a higher hazard of death.[10] The NT-pro-BNP level at baseline reflects the risk stratification of patients with LtR-shunt CHD-associated PAH, and those who had higher NT-pro-BNP levels would have to intensify therapy which affected the outcome at follow-up. Therefore, the prognostic value of NT-pro BNP level may be more significant if serial measurement was performed during follow-up.

Our study showed that cardiac index value <2.5 l/min/m2, which is associated with parameters of intermediate and high-risk prognostic stratification in PAH3, had independently increased the risk of mortality in LtR-shunt CHD-associated PAH. Based on cardiac index, there are three risk categories: low risk (cardiac index ≥2.5 l/min/m2), intermediate risk (cardiac index 2.0-2.4 l/min/m2, and high risk (cardiac index <2.0 l/min/m2). Because of the insufficient number of subjects, we divided into two categories by combining intermediate and high-risk into one group (cardiac index <2.5 l/min/m2). Other previous studies indicated similar findings.[1,9,10,11] Cardiac index was measured during RHC, which is an invasive procedure not always available in non-PH centers. This measurement was usually performed only at the baseline or diagnostic level, therefore repetitive measurement is not feasible, even in several PH centers in our region. Therefore, the baseline cardiac index calculation must be performed as an important predictor for mortality in adult patients with LtR-shunt CHD-associated PAH.

Our study indicated that baseline systolic blood pressure was an independent predictor for mortality. Earlier studies showed that systolic blood pressure <100 mmHg was a significant independent risk factor for mortality in PAH patients after adjusting for age and underlying diagnosis.[12] The reduced systolic blood pressure closely correlated with lower blood sodium levels, which also posed as a significant predictor for mortality.[12] This implicated the neurohormonal activation in the setting of low cardiac output.[12] In PAH, the sympathetic activation was exaggerated and suggested to influence the hemodynamic, a process similar to left heart failure.[13] Deteriorating right ventricular function in PAH-induced sympathetic activation, which if it lasts for a long time may change the myocardial structure and function. Eventually sustained low blood pressure, along with life-threatening arrhythmias, affects the fatal outcomes in these patients.[14,15] Once reduced systolic blood pressure occurred in the index of PAH diagnosis,

it informed the future risk of mortality.

The result of our study may represent the broader population of CHD-associated PAH which is still prevalent in Indonesia. However, national data regarding the prevalence and the prognosis of different CHD-associated PAH phenotypes and the role of risk stratification in prognostication is necessary to be collected and analyzed.

There are several limitations of this study. Firstly, the study used a retrospective cohort analysis design and was based on a single-center registry. Second, there were several data that were not fully recorded in the medical records. Third, with a fairly long follow-up period from July 2012 to October 2020, there were a number of patients who were lost to follow-up so it was not known whether these patients survived or died. Fourth, for patients with PDA, the recording of the lower extremity for oxygen saturation and blood pressure was necessary to be analyzed.

Conclusions

There were three independent predictors for mortality in adult patients with left-to-right intracardiac shunt CHD-associated PAH, namely systolic blood pressure <100 mmHg, cardiac index <2.5 L/min/m2 and the presence of Eisenmenger syndrome at the index of PAH diagnosis.

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Declaration of Conflict of Interest

All the authors declare no conflict of interest.

List of Abbreviations

ASD	Atrial Septal Defect
CHD	Congenital Heart Disease
NT-ProBNP	N-Terminal Pro-B-Type Natriuretic Peptide
PDA	Patent Ductus Arteriosus
PAH	Pulmonary arterial hypertension
RHC	Right Heart Catheterization
VSD	Ventricle Septal Defects

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Original Article

Tailored BEST Exercise Protocol in Heart Failure Rehabilitation: Intracardiac and Extracardiac Benefits for All Responders

Kevin Triangto,[1,2]* Basuni Radi,[1,2,3] Bambang B. Siswanto,[1,2,3] Tresia FU. Tambunan,[1,4] Teuku Heriansyah,[5] Alida R. Harahap,[1] Aria Kekalih,[6] Hajime Katsukawa,[7] Ade Meidian Ambari,[2,3] Dwita Rian Desandri,[2,3] Bambang Dwiputra,[2,3] and Anwar Santoso.[2,3]

Abstract

Introduction: Heart failure with a reduced ejection fraction (HFrEF) significantly contributes to global morbidity and mortality, necessitating effective rehabilitation programs. Exercise-based rehabilitation improves functional capacity and quality of life in HFrEF patients, though responses vary. The tailored BEST (Breathing, Endurance, and Strengthening) exercise protocol addresses both cardiac and extracardiac rehabilitation, benefiting all patients regardless of response status. This study evaluated the protocol's effects on HFrEF patients and classified rehabilitation responses based on changes in aerobic capacity.

Methods: In this etiologic study with a prospective cohort design, all participants underwent a three-month cardiac rehabilitation program using the BEST Exercise Protocol. Assessments included the 6-minute walk test (6MWT), short physical performance battery (SPPB), handgrip strength, chest expansion, ultrasonographic measurements, and NT-proBNP levels before and after the intervention, with statistical comparisons made within and between groups. Groupings of responder level will be reliant on 6MWT distance achievement at the end of the program, with ≥6% improvement classified as good responders.

Results: Out of 107 HFrEF patients (median age 55 years, ejection fraction 29.50±7.34%), 63.56% were good responders and 36.44% were poor responders (<6% improvement). Good responders showed significant improvements in most extracardiac parameters, including a 20% increase in 6MWT distance (470.96±69.21 meters post-rehabilitation), chest expansion, handgrip strength, and SPPB scores ($p<0.001$ for all). Poor responders also improved in chest expansion, sit-to-stand time, and postural balance, with minor 6MWT gains (407.33±72.50 meters). NT-proBNP levels decreased in both groups but were not statistically significant ($p=0.288$ and 0.368 for good and poor responders, respectively).

Conclusion: The tailored BEST Exercise Protocol offers substantial cardiac and extracardiac benefits for HFrEF patients by enhancing functional capacity and muscle strength. Both good and poor responders exhibited significant improvements, indicating the protocol's broad applicability. However, the lack of statistically significant NT-proBNP reduction suggests further studies on cardiac biomarkers are needed. The 6MWT provides accessible rehabilitation insights, though more precise evaluations like Cardiopulmonary Exercise Testing (CPET) can offer clearer insights into cardiopulmonary adaptations.

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Keywords: *Heart failure with reduced ejection fraction (HFrEF); Endurance Exercise; Breathing Exercise; Strengthening Exercise; Heart failure rehabilitation.*

[1] Doctoral Program in Medical Sciences, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
[2] National Cardiovascular Center Harapan Kita, Jakarta, Indonesia;
[3] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.
[4] Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.
[5] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia.
[6] Department of Community Medicine, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
[7] Department of Scientific Research, Japanese Society for Early Mobilization, Tokyo, Japan.

Correspondence:
Kevin Triangto, Doctoral Program in Medical Sciences, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
Email: kevintriangto14@gmail.com.

Introduction

Heart failure with reduced ejection fraction (HFrEF) is a prevalent condition associated with significant morbidity and mortality that necessitates effective rehabilitation strategies.[1] Exercise-based cardiac rehabilitation programs have shown promise for improving the functional capacity and quality of life of patients with HFrEF.[2] The breathing, endurance, and strengthening (BEST) protocol aims to optimize cardiovascular and muscular adaptations using a tailored approach.[3,4] This personalized exercise regimen may address the diverse needs of patients with HFrEF and potentially lead to better outcomes across a broader spectrum of responders.

Initially, the ARISTOS-HF trial demonstrated the importance of a comprehensive exercise program in patients with HFrEF.[4] This program combines endurance, resistance, and inspiratory muscle training.[4] Endurance exercises focus on improving cardiovascular endurance and overall aerobic capacity.[4] Breathing exercises target strengthening of the respiratory muscles to enhance lung function.[4] Strengthening exercises aim to increase muscle mass and improve overall muscle strength and endurance.[4]

The study's findings revealed that the combined Aerobic, Resistance, and Inspiratory Strengthening (ARIS) program yielded superior benefits compared to aerobic alone or aerobic combined with either resistance or inspiratory muscle strengthening, as they would affect the extracardiac ergoceptors.[2,3,5] The ARIS group showed trends towards greater improvement in aerobic capacity, with a 19% increase in peak VO2 compared to 9-11% in the other groups.[4] Additionally, the combined program demonstrated significant benefits in terms of cardiac function, aerobic capacity, quality of life, respiratory function, and skeletal muscle function.[4,5] These results support the muscle training hypothesis for HFrEF, suggesting that addressing multiple aspects of physical fitness through a combined training approach would eventually provide optimal benefits for patients with HFrEF.5 Unfortunately, the ARISTOS study did not classify rehabilitation responder levels, which has been shown to affect rehabilitation impacts between subjects.[6,7]

Despite the increasing body of evidence supporting its benefits, HFrEF rehabilitation continues to face numerous barriers, exhibits low participation rates, and the optimal exercise protocol with individualization of rehabilitation programs remains unclear.[6,8–10] In addition to insufficient knowledge regarding exercise safety for patients with HFrEF between care providers, another contributing factor is the low proportion of favorable responders after a three-month rehabilitation period, resulting in minimal or no improvement in aerobic capacity as depicted by VO2 max upon program completion.[8,11,12] This study aimed to address this knowledge gap by investigating the impact of a tailored rehabilitation program based on the BEST Exercise protocol on both intracardiac and extracardiac outcomes in patients with HFrEF, and presenting the number of good and poor responders while exhibiting which extracardiac factors had obtained the best improvement. The rationale is to provide evidence-based recommendations for designing individualized rehabilitation programs that improve the overall physical function and quality of life in patients with HFrEF. We hypothesize that this tailored BEST protocol in HF rehabilitation will significantly improve cardiac and extracardiac parameters among patients with HFrEF, regardless of their responder status.

Methods

Study Participants

From April 2022 to April 2023, the research group initially screened 125 patients in the Holistic Assessment and Rehabilitation toolKIT for Heart Failure (HARKIT-HF) cohort. Of these, 107 individuals with HFrEF were selected for the study after completing a 3-month cardiac rehabilitation program. These participants were all rehabilitation patients between 18 and 65 years of age who had been diagnosed with chronic HFrEF by their cardiologist. Prior to rehabilitation referrals, all patients had received optimal guideline-directed medical therapy (GDMT) for at least two months. These individuals had to achieve hemodynamic stability for a minimum of one week following their most recent hospitalization before being included in the program. Regarding etiology, only ischemic and cardiomyopathy causes of HFrEF were included, whereas severe valvular disorders and congenital heart disease were excluded from the study.

Subjects were also excluded if they experienced impaired mobility due to neuromuscular conditions, amputation, or severe pain that hindered their movement.

Examination

This etiologic study had a pre-post design in which all subjects received the same BEST exercise protocol for three months, 2-3 days per week in a structure-based rehabilitation facility. Before enrollment in the program, subjects underwent initial measurements of cardiac parameters, including echocardiographic values, such as left ventricular ejection fraction (LVEF) and tricuspid annular plane systolic excursion (TAPSE). Subjects had their physical parameters measured, namely, 6-minute walk test (6MWT) distance, handgrip strength, chest expansion, and short physical performance battery (SPPB). Supporting diagnostics such as ultrasonographic parameters (diaphragm thickness during inspiration and expiration, anterior forearm muscle thickness) and laboratory values (NT-proBNP) were additionally assessed pre-post to enhance the overall results. The above parameters will be measured before and after the completion of the rehabilitation program by 3 months. Follow-up protocol includes measurement of all the components, being both physical and laboratory examinations. All measurements were standardized to mitigate measurement bias. Responder categories were stratified based on the improvement in 6MWT distance at the end of the program as previously published within the HF-ACTION study chain, with those demonstrating an improvement of ≥6% classified as good responders.[9]

Ethical Clearance Statement

The National Cardiovascular Center Harapan Kita Institutional Review Board granted ethical clearance for this study (Approval Number: DP.04.03/KEP238/EC105/2023), and informed consent was obtained from all participants prior to assessments.

Exercise Protocol

A description of the BEST exercise protocol (Figure 1) begins with breathing exercises that involve 10 min of deep breathing in a corrective thoracal posture combined with upper extremity range of motion exercise to optimize chest expansion. Endurance exercise began with 10 min of warm-up through general flexibility exercises for the upper and lower extremities, followed by 20 min of core exercise through brisk walking or treadmill exercise at moderate intensity (40-59% Heart Rate Reserve). Subjective maintenance of aerobic intensity was performed through a talk test to ensure that the patient could converse in full sentences while performing the required exercise intensity. The last element consisted of strength training exercises conducted on alternating days each week. On one day, the session targeted major upper body muscles (pectorals, deltoids, biceps, triceps, and forearm) using lightweight dumbbells of 1-2 kg, with participants performing three sets of 10-12 repetitions for each exercise. On other days, the session focused on the major core and lower body muscles (gluteus, quadriceps, hamstring, and latissimus dorsi), employing calisthenics and chair-based exercises. Details on all the strengthening exercises can be seen in Table 1. Overall, the patient received 3-5 days of breathing and endurance exercises, and 1-2 days of strengthening exercises on alternating days for each major muscle group, as recommended by the ESC guidelines. The patient had to complete the program for 3 months before undergoing a follow-up examination of all intra- and extracardiac parameters.

Statistical Analysis

SPSS for Macintosh version 29.0 (IBM, New York, USA) was used for the statistical analysis in this study. The Kolmogorov-Smirnov test was initially used to examine all numeric data for a normal distribution. Most variables in the study were continuous and thus expressed as mean±SD or median (minimum-maximum values), while categorical variables are shown as proportions with percentages. To compare between responder groups, independent Student's t-test and Mann-Whitney U test were used, while intragroup comparisons were analyzed with dependent Student's t-test and Wilcoxon test. Spearman correlation analysis was used to evaluate nonparametric NT-proBNP values in relation to extracardiac parameters.

Results

The study recruited 107 subjects with baseline characteristics and changes after three months of

Table 1. Protocol of Strengthening Exercises.

No.	Upper Extremities Exercises	Form and Weight	Muscles Affected	Lower Extremities Exercises	Form	Muscles Affected
1	Core Sides	1 kg Dumbbell Side Bends	Ext Obliques and Quadratus Lumborum	Core Extension/ Flexion	Wood Chop Exercise and Trunk Extension	Rectus Abdominis and Erector Spinae
2	Shoulder Abduction/ Adduction	Shoulder raise with 1 kg Dumbbells	Middle Deltoids and Rotator Cuff	Hip Abduction/ Adduction	Standing Hip Abduction	Adductor group and Tensor Fascia Latae
3	Shoulder Flexion/ Extension	Shoulder press with 1 kg Dumbbells	Anterior Deltoid, Biceps, Triceps	Hip Flexion/ Extension	Squat and Lunges	Iliopsoas, Gluteus
4	Rhomboids Retraction	Bent over row with 1 kg Dumbbells	Rhomboids, Latissimus Dorsi	Knee Flexion	Standing Hamstring Curls	Hamstring
5	Elbow Flexion/ Extension	Curl exercise with 1 kg Dumbbells	Biceps, triceps	Knee Extension	Seated Leg Extension	Quadriceps
6	Wrist Flexion/ Extension & Deviation	Hammer exercise 1 kg Dumbbells	Forearm Flexors – Extensors	Ankle Dorsi/ Plantarflexion	Standing	Gastrocsoleus and Anterior Tibialis

Figure 1. BEST exercise Protocol graphical representation .

Table 2. Patient baseline characteristics and overall improvement.

Variables	Baseline (n=107)	After 3 months CR (n=107)	Mean Difference±SD	p-value
Age (years)	55 (39-65)			
Female (n,%)	10 (9.35%)			
BMI (kg/m2)	26.44±4.90	26.46±4.93	0.01±0.43	0.739b,
Ejection fraction (%)	29.50±7.34	31.15±7.20	1.83±3.50	<0.001b,*
TAPSE (mm)	17.86±4.81	17.91±4.71	0.05±0.44	0.223b
6MWT (m)	395.74±61.54	447.77±76.54	52.03±63.62	<0.001b,*
Baseline heart rate (bpm)	78.20±13.63	79.29±13.69	1.09±11.82	0.318b
Post-6MWT heart rate (bpm)	99.42±16.86	103.72±19.67	4.30±17.76	0.014 b,*
Full tandem balance (seconds)	9.92±2.74	11.48±1.74	1.56±2.75	<0.001b,*
4-meter gait (seconds)	2.33±0.49	2.25±0.45	–0.08±0.41	0.047b,*
Gait speed (m/s)	0.58±0.12	0.56±0.11	–0.02±0.10	0.047b,*
5-times sit to stand (seconds)	12.24±3.82	8.72±3.22	3.52±3.66	<0.001 b,*
SPPB composite score (max 15)	11 (7-12)	12 (8-12)		<0.001c
Superior Chest Expansion (cm)	2.19±0.88	2.68±0.73	0.49±0.95	<0.001b,*
Inferior Chest Expansion (cm)	2.80±1.25	2.68±0.72	0.60±1.87	<0.001b,*
Dominant HGS (kg)	30.28±7.73	31.43±7.67	1.15±4.09	0.004b,*
Non-dominant HGS (kg)	28.15±7.94	29.25±8.59	1.10±4.34	0.010b,*
Tidal Inspiration Thickness	0.26±0.09	0.26±0.09	–0.00±0.08	0.972
Tidal Expiration Thickness	0.19±0.05	0.18±0.06	–0.00±0.65	0.549
Deep Inspiration Thickness	0.41±0.15	0.45±0.15	0.04±0.16	0.004
Deep Expiration Thickness	0.21±0.07	0.21±0.14	0.01±0.14	0.652
Dominant forearm thickness (cm)	2.20±0.57	2.16±0.52	–0.03±0.63	0.589b
Non-dominant forearm thickness left (cm)	2.11±0.54	2.30±0.170	0.18±1.80	0.291b
NT-proBNP (pg/ml)	816 (105-69230)	785 (105-50297)		0.172c

6MWT: 6-minute walk test; BMI: Body mass index; HGS, handgrip strength; SPPB, short physical performance battery; TAPSE, tricuspid annular plane systolic excursion.
All values are expressed as mean±SD, median (min-max), or number of cases (%).
an Analyzed using the Mann-Whitney U test
b Analyzed using independent Student's t-test
c Analyzed using Fisher's exact test
* Statistically significant at p=0.05.

rehabilitation completion, as shown in Table 2. Study demographics include a median age of 55 years, 9.35% are female, with a slightly obese BMI (26.44±4.90 kg/m2), and a reduced ejection fraction of 29.50±7.34%. It appeared that both responder levels combined significantly improved several parameters. Intracardiac changes include an increased post-6MWT heart rate by 4.30 beats, yielding a significantly higher 6MWT distance of 447.77±76.54 (improved 52.03±63.62, p<0.001). Functional testing with the SPPB also showed statistically significant improvement in all three components: postural balance, gait speed, 5-times sit-to-stand, and overall SPPB composite score. Among these improvements, 5 times sit-to-stand obtained the highest mean difference, with a reduction of 3.52±3.66 seconds compared to their baseline level. Extracardiac improvements could be seen in both respiratory and musculoskeletal components, as seen in chest expansion, which also improved in both superior and inferior measurements, as well as increased bilateral handgrip strength. Ultrasonographic measurements revealed a significant improvement only in diaphragmatic deep inspiration thickness. No statistically significant finding was observed in NT-proBNP improvement, although a trend toward lower values was noted after completion of rehabilitation.

The majority of the sample comprised good responders (63.56%), and approximately one-third

Table 3. The bivariate analysis of variables as predictors of mortality in patients with LtR-shunt CHD-associated PAH.

Variables	Poor Responder (n=39)			Good Responder (n=68)			After CR
	Baseline	After 3 months CR	Intragroup p-value	Baseline	After 3 months CR	Intragroup p-value	Intergroup p-value
Age (years)	53 (39-65)			56 (29-65)			0.038c
Female (n,%)	3 (7.69%)			7 (10.29%)			0.744e
BMI (kg/m2)	27.43±5.83	27.41±5.87	0.794b	25.88±4.22	25.91±4.25	0.556b	0.167a
Ejection fraction (%)	29.78±7.20	30.67±7.15	0.013b,*	29.34±7.46	31.43±7.27	<0.001b,*	0.602a
TAPSE (mm)	17.96±5.06	17.94±4.98	0.696b	17.80±4.69	17.89±4.58	0.137b	0.959a
6MWT (m)	410.26±61.44	407.33±72.50	0.595b	387.41±60.47	470.96±69.21	<0.001b,*	<0.001a,*
Baseline heart rate (bpm)	81.74±15.79	82.92±17.15	0.534b	76.16±11.89	77.21±10.85	0.441b	0.066a
Post-6MWT heart rate (bpm)	103.03±17.02	100.28±24.39	0.377b	97.35±16.43	105.69±16.24	<0.001b,*	0.086a
Full tandem balance (seconds)	9.86±3.02	10.81±2.63	0.039b,*	9.95±2.58	11.86±0.67	<0.001b,*	0.010a
4-meter gait (seconds)	2.28±0.50	2.32±0.51	0.557b	2.36±0.49	2.21±0.41	0.005b,*	0.118a
Gait speed (m/s)	0.57±0.12	0.58±0.13	0.557b	0.59±0.12	0.55±0.10	0.005b,*	0.095a
5-times sit to stand (seconds)	11.96±3.84	9.33±4.18	<0.001b,*	12.40±3.83	8.36±2.47	<0.001b,*	0.095a
SPPB composite score (max 15)	11 (7-12)	12 (8-12)	<0.001d,*	11 (8-12)	12 (10-12)	<0.001d,*	0.024c
Superior Chest Expansion (cm)	2.31±0.99	2.60±0.49	0.023b,*	2.12 ±0.80	2.72±0.83	<0.001b,*	0.180a
Inferior Chest Expansion (cm)	2.98±1.44	3.40±1.87	0.253b	2.70±1.12	3.39±1.16	<0.001b,*	0.486a
Dominant HGS (kg)	30.57±7.98	31.06±8.66	0.392b	30.12±7.65	31.65±7.11	0.005b,*	0.353a
Non-dominant HGS (kg)	28.48±9.10	28.27±10.54	0.796b	27.96±7.27	29.81±7.27	<0.001b,*	0.187a
Tidal Inspiration Thickness	0.25±0.08	0.25±0.10	0.679b	0.26±0.09	0.27±0.08	0.787b	0.148a
Tidal Expiration Thickness	0.19±0.06	0.19±0.08	0.890b	0.19±0.05	0.18±0.05	0.252b	0.355a
Deep Inspiration Thickness	0.43±0.16	0.43±0.18	0.938b	0.40±0.15	0.47±0.14	<0.001b,*	0.092a
Deep Expiration Thickness	0.21±0.08	0.23±0.20	0.571b	0.20±0.07	0.20±0.86	0.949b	0.172a
Dominant forearm thickness (cm)	2.26±0.61	2.12±0.53	0.130b	2.16±0.55	2.19±0.52	0.716b	0.258a

Non-dominant forearm thickness (cm)	2.17±0.55	2.61±2.73	0.339b	2.08±0.53	2.11±0.49	0.650b	0.071a
NT-proBNP (pg/ml)	1139 (105-7484)	895 (105-13790)	0.368d	701 (119-69230)	573 (119-50927)	0.288d	0.389c

performance battery; TAPSE, tricuspid annular plane systolic excursion.
All values are expressed as mean±SD, median (min-max), or number of cases (%).
a Analyzed using independent Student's t-test
b Analyzed using dependent Student's t-test
c Analyzed using Mann-Whitney U test
d Analyzed using Wilcoxon test
e Analyzed using Fisher's exact test

were classified as poor responders (36.44%); these comparisons are presented in detail in Table 3. The patient's age was younger in poor responders by 3 years, and the majority of subjects were male, with less than 15% of the sample being female. Similar baseline values were observed in EF, ranging below 30% and TAPSE < 18 mm in both groups. After completing rehabilitation, EF seemed to significantly improve in both groups (p< 0.05), although changes were mild and still classified as reduced (below 40%), good responders vividly show better improvement. Distance obtained in 6MWT was significantly different in between groups, after 3 months obtaining 407.33±72.50 in poor responder, as compared to 470.96±69.21 in good responder, where good responder had improved approximately 20% from baseline. Good responders had an overall significant improvement in all components of the SPPB, namely balance, gait speed, and sit-to-stand time (p ≤ 0.001, 0.005, and <0.001, respectively), while poor responders did not achieve statistical significance in gait speed improvement. The SPPB composite scores were significantly different (p=0.024), with a minimum value of 10 in good responders and 8 in poor responders. The difference in the SPPB scores appeared to be influenced by the balance score, as it differed significantly between the groups (p=0.010), and the other two components did not reach statistical significance.

Chest expansions were seen to significantly improve in both superior and inferior measurements in good responders after rehabilitation completion, while poor responders also achieved overall improvement. Only superior measures were seen to be statistically significant. Similarly, musculoskeletal improvements were observed in both dominant and non-dominant HGS, obtaining an overall significant improvement in the good responder group, while only achieving an improvement trend in the other group. Regarding ultrasonographic parameters in both the diaphragm and anterior forearm measurements, only deep diaphragmatic inspiration thickness demonstrated a statistically significant improvement of approximately 17% in the good responder group, whereas the other parameters displayed trends of improvement. Despite these changes in both the respiratory and musculoskeletal systems, there was no significant difference in the final measurements between the groups. A graphical summary of improvement after 3-months between the responders is shown in Figure 2, where good responders showed an overall statistically significant improvement in most extracardiac components, except for NT-proBNP in the good and poor responder groups, as they were generally reduced after three months without reaching statistical significance (p=0.288 and 0.368, respectively). In contrast, poor responders also showed significant improvements in superior chest expansion, sit-to-stand time (depicted by lower extremity muscle strength), and postural balance.

Discussion

This study recruited 107 subjects with heart failure with reduced ejection fraction HFrEF to evaluate the effect of the BEST Exercise protocol on both cardiac and extracardiac outcomes. The cohort's median age was 55 years, with 9.35% female participants, and a mean BMI reflecting a mildly obese population (26.44±4.90 kg/m^2). All these showed a highly contrasting population, as the present cohort is much younger, highly predominant

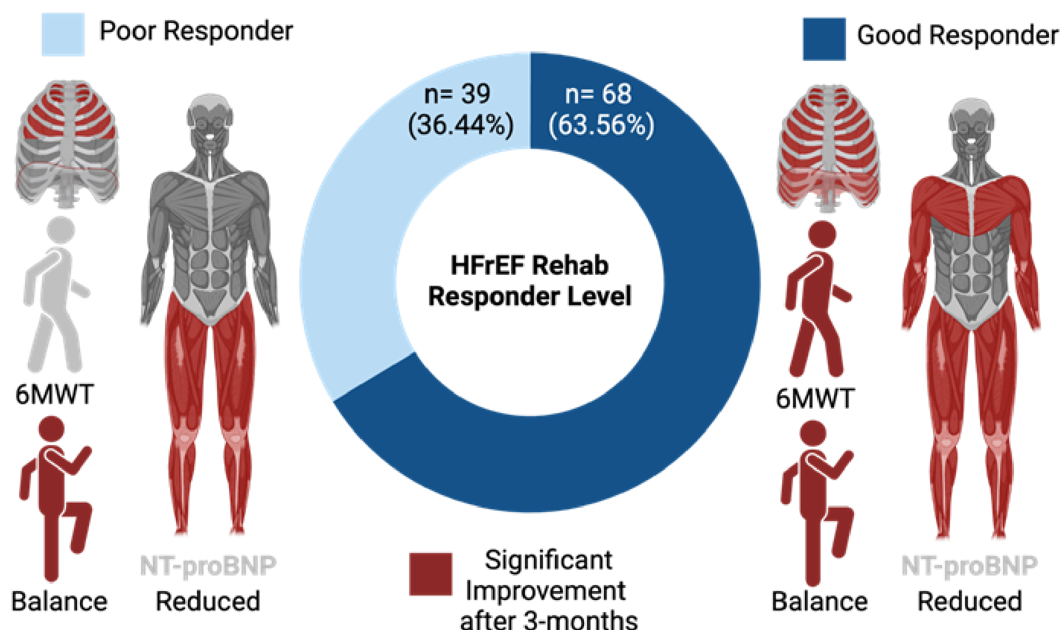

Figure 2. Graphical representation of significant improvements in all rehabilitation responder levels.

in males, and leaner compared to the previous similar study by Bakker with a median of 63 years, 69-81% males, and a BMI of 29±5.0 kg/m². Bakker et al. performed a similar study that defined both good and poor responders; their study also included HFpEF (approximately 30%), while the present study recruited only HFrEF subjects, thus presenting a higher severity of mean ejection fraction of 29.50±7.34%, indicating a younger yet notable cardiac impairment.[6] A similar interventional study by Laoutaris also reported an older age group with a mean of 63.9 years and the youngest being 59 years.[4] Within the highly classified population, the proportion of responders was the majority of good responders (63.56%), which was also in contrast to a previous study with only 45.16% of good responders.[6] Previous studies have also highlighted the differences between Asian HF and global epidemiology, and the current novel findings showed that the younger cohort exhibited a distinct characteristic, potentially possessing superior physical capacity, which may result in greater benefits from cardiac rehabilitation.[2]

Another study by Schutter et al., despite not being performed on an HF-specific cohort, touched upon younger age as a non-modifiable factor that leads to a better rehabilitation response, and conversely, a higher baseline VO2 would predispose to an inferior rehabilitation response.[7] These implications were seen vividly in the present cohort, as the good responder had initially lower baseline 6MWT when compared with the poor responder (387.41±60.47 m vs. 410.26±61.44 m respectively), with a substantially higher final 6MWT distance after rehabilitation completion (470.96±69.21 m vs. 407.33±72.50 m). Additionally, it could be seen that the younger cohort had a higher baseline 6MWT distance, which had not been reported previously in other published Asian HF studies that displayed varying results from 245.39±96.69 m in Indonesia,[13] 270 (180-367) m in Japan,[14,15] 312±92 m in Singapore,16 270.12±78.93 m in India,[17] and 150-450 m in China,[18] where almost all the published studies had a mean age of >60 years. In accordance with the most recent study on sarcopenia assessed using the Asian Working Group for Sarcopenia 2019 criteria, a 6MWT distance <300 m and HGS <28 kg were used as cutoff values

to classify frailty.[14] When applied to the present study, it is apparent that the majority of the subjects can be categorized as robust, obtaining a baseline 6MWT of 387.41±60.47 m, and dominant HGS of 30.12±7.65 kg. Another cut-off study by Aida et al. emphasized the role of physical examination in older HF subjects with a median of 75 (71-80) years, which also supported the present results with 6MWT distance <400 m cut-off could be represented with HGS of 21.9 kg, both of which have been surpassed by the good and poor responder cohorts in the present study, being aligned with the robust physical capacity.[19] All of these studies showed how 6MWT distance is correlated with a better profile of extracardiac parameters, such as HGS.

Both good and poor responders exhibited significant improvements in extracardiac outcomes, although these improvements were more pronounced in good responders (Figure 2). Good responders showed statistically significant improvements in chest expansion, handgrip strength on both sides, short physical performance battery (SPPB), and 6MWT results after completion of rehabilitation using the BEST protocol. In contrast, poor responders demonstrated meaningful improvements in superior chest expansion, lower extremity muscle strength, and postural balance. It should be noted that ergo reflex is a key mechanism in heart failure that modulates cardiovascular and respiratory responses during physical activity.[5] It was previously shown that patients with HF may have diaphragmatic dysfunction due to systemic inflammation, increased peripheral resistance, and immobility in the HF pathology continuum.[20] Similarly, the majority of skeletal muscle dysfunction in patients is caused by increased peripheral resistance and low cardiac output, together often manifesting as myopathy, thus increasing ergoreflex sensitivity.[5] This heightened sensitivity, elicited by muscle contraction (mechanoreflex) through the musculoskeletal system and metabolite accumulation (metaboreflex) mediated by acid-base balance through the respiratory system, results in abnormal cardiovascular responses such as excessive vasoconstriction and increased heart rate.[3,5] Breathing exercises can help strengthen respiratory muscles and improve ventilatory efficiency, whereas strengthening exercises reduce muscle wasting and lower ergoreflex sensitivity by improving muscle function.[3–5,20] Essentially, endurance exercise improves peak oxygen uptake (VO2) and reduces sympathetic overactivity, helping to enhance cardiovascular efficiency; thus, it should always be prescribed for HF patients.[4,5,21] Together, these exercises restore a balanced autonomic response, enhance exercise tolerance, and alleviate HF symptoms, making the BEST protocol a key component of HF rehabilitation.[5,21]

Interestingly, the intracardiac biomarker NT-proBNP was reduced in both groups, in agreement with a previous meta-analysis.[22] Nevertheless, these reductions were not statistically significant, indicating that the effect of the exercise protocol on this cardiac biomarker may necessitate further investigation and potentially require the examination of additional biomarkers. A limitation of this study was the reliance on the 6MWT instead of cardiopulmonary exercise testing (CPET) with breath-by-breath analysis.[23] While the 6MWT is a more accessible and practical tool for clinical application, the CPET provides a more detailed and accurate assessment of cardiopulmonary function, which could offer deeper insights into the physiological changes induced by the BEST protocol. However, a previous study showed that utilization of the 6MWT distance with the Cahalin formula in HF subjects had sufficient correlation strength with CPET maximal oxygen uptake outputs.[24] Additionally, the use of 6MWT distance in HF aligns with real-world clinical settings, making the study's findings more applicable to general practice.[19] Another strength of this study lies in its focus on younger patients with HF, which is a novel category, demonstrating that the BEST protocol can lead to significant improvements in both intracardiac and extracardiac outcomes even in poor responders.

Conclusion

In conclusion, the Tailored BEST Exercise Protocol in heart failure rehabilitation demonstrated significant intracardiac and extracardiac benefits for both good and poor responders after three months of intervention. The majority of the study population was classified as good responders (63.56%), who exhibited statistically significant improvements in most extracardiac components, including chest expansion, handgrip strength, the 6-minute walk test (6MWT), and the short physical performance battery (SPPB), with the exception of NT-proBNP, which showed trends of

reduction in both groups without statistical significance. Notably, poor responders, who comprised 36.44% of the sample, also achieved substantial improvements in superior chest expansion, sit-to-stand performance (indicating enhanced lower-extremity muscle strength), and postural balance. These findings highlight that even among poor responders, substantial extracardiac functional gains can be achieved, underscoring the broad applicability and efficacy of the protocol in heart failure rehabilitation. Further investigation is required to examine the long-term effects of tailored exercise interventions on NT-proBNP and other biomarkers to validate these findings.

Conflict of Interest

Hajime Katsukawa receives a salary from the Japanese Society for Early Mobilization (a nonprofit society) as a chair (full-time). All the other authors have declared that no competing interests exist.

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List of Abbreviations

6MWT	6-minute walk test
BEST	Breathing, Endurance, and Strengthening
CPET	Cardiopulmonary Exercise Testing
HF	Heart Failure
HFrEF	Heart Failure with reduced Ejection Fraction
LVEF	Left Ventricular Ejection Fraction
NT-ProBNP	N-Terminal Pro-B-Type Natriuretic Peptide
SPPB	Short Physical Performance Battery
TAPSE	Tricuspid Annular Plane Systolic Excursion

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Original Article

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Examining the Specificity of Smartphone Based ECG Devices in Decision–Making for ST–Elevation Myocardial Infarction and Non–ST–Elevation Myocardial Infarction

Sahil Mahajan,[1] Salil Garg,[1] Yogendra Singh,[2] Richa Sharma,[1] Nitin Chandola,[3] Tanuj Bhatia,[1] Deeksha Agarwal.[4]

[1] Department of Cardiology, Shree Mahant Indresh Hospital, Dehradun, India.
[2] Department of Cardiology, Max Super-specialty Hospital, Dehradun, India.
[3] Department of Research and Development, Sunfox Technologies Pvt. Ltd, Dehradun, India.
[4] Department of Research and Technology, Sunfox Technologies Pvt. Ltd, Dehradun, India.

Correspondence:
Nitin Chandola, Department of Research and Development, Sunfox Technologies Pvt. Ltd, Dehradun, India.
Email: nitinchandola7@gmail.com

Abstract

Background & Objectives: Electrocardiography (ECG) stands as a cornerstone diagnostic tool for assessing cardiac health, particularly in ruling out abnormalities. The integration of smartphone devices presents a promising avenue for expedited detection of cardiac irregularities. This study aims to evaluate the diagnostic efficacy of smartphone ECG devices in subjects admitted to Cardiac Care Units (CCUs) and Cardiac Intensive Care Units (CICUs).

Methods: A retrospective analysis was conducted on a cohort comprising 62 patients presenting with cardiac symptoms. Utilizing smartphone ECG devices as the index, 12-lead ECG tests were administered alongside the Gold Standard ECG machine for comparison among patients in CCUs and CICUs. Diagnostic decisions concerning the presence of ST-Elevation Myocardial Infarction (STEMI) or Non-ST-Elevation Myocardial Infarction (NSTEMI) were made by a team of cardiologists following a meticulous review of both sets of ECG reports.

Results: Data analysis was conducted on 56 patients. The smartphone-based ECG device exhibited 100% specificity, 93% sensitivity, 80% Negative Predictive Value, and 100% Positive Predictive Value, yielding an F-score of 0.96 and a Mathew Correlation Coefficient value of 0.86.

Discussions: This study unequivocally underscores the significant potential of the Spandan ECG device in accurately identifying a range of cardiac abnormalities, including critical conditions such as STEMI and ischemia. Despite its portable nature, smartphone ECG technology demonstrates utility within Critical Care Units for timely monitoring and diagnosis.

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Keywords: *Digital health, Electrocardiography, mHealth, Ischemia, Smartphone ECG, ST-elevation myocardial infarction.*

Introduction

India currently grapples with the highest prevalence of acute coronary syndrome (ACS) and ST-segment elevation myocardial infarction (STEMI) globally. Alarming statistics from 2013 highlight 261,694 deaths, marking a disturbing surge of 138% since 1990, indicating a significant and concerning dimension within India's healthcare landscape. Compared to other ethnic groups, Indians exhibit a higher likelihood of hospitalization for coronary artery disease (CAD) complications, with admission rates 5–10 times higher for individuals under 40.[1] STEMI represents a critical and often fatal form of myocardial infarction characterized by the occlusion of one or more coronary arteries, resulting in severe reduction or cessation of blood flow to the heart muscle. Typically, this acute event is precipitated by the rupture, erosion, fissuring, or dissection of coronary artery plaques, culminating in the formation of an obstructive thrombus. Primary factors contributing to ST-elevation myocardial infarction include dyslipidemia, diabetes mellitus, hypertension, tobacco use, and familial history of coronary artery disease.[2-3] The timely diagnosis of STEMI is imperative, directly impacting mortality and morbidity rates. Swift recognition and intervention significantly enhance the anticipation of positive outcomes for patients. As the electrocardiogram (ECG) remains the most widely employed and accessible diagnostic tool for STEMI, there is an intriguing postulation that making reliable ECGs readily available to high-risk outpatient populations could profoundly impact outcomes. Such an approach holds the potential to substantially mitigate delays in early diagnosis and subsequent treatment, facilitating the expeditious implementation of life-saving revascularization procedures.[4]

ST-segment elevation serves as a crucial diagnostic marker discerned in the 12-lead ECG. When ST elevation is observed, the ECG becomes pivotal in ascertaining the occurrence of STEMI. This diagnostic tool records the intricate electrical patterns of the heart, offering invaluable insights into cardiac health.[5-7]

The 12-lead ECG plays a pivotal role in patient care, particularly in emergencies, aiding in diagnosis and guiding medical interventions. Therefore, it is of utmost importance for healthcare professionals to promptly identify STEMI-related episodes and incidents.[8]

Table 1. Baseline demographics and clinical characteristics of the participants.

Variables	Number	Percentage (%)
Gender- Male	61	98.3%
Hypertensive	7	11.2%
Smoker	4	6.45%
Diabetic	13	20.9%
CAD	52	83.8%
Pacemaker implant	1	1.61%
Stent implant	36	58%
Chest Pain	8	12.9%
Shortness of Breath	5	8.06%

To date, smartphone-based ECG machines have been extensively studied for screening arrhythmias and myocardial infarctions in clinical settings. However, their presence in intensive care units for diagnostic usage remains limited. A smartphone-based portable ECG device (SPANDAN PRO) that is capable of taking lead 12 lead ECGs by using derived ECG methods. The Spandan portable ECG (Sunfox Technologies Pvt. Ltd.) device connects to a smartphone via an application interface, as shown in Figure. 1. The Spandan device, a smartphone-based 12-lead, single-channel device, was utilized in this study for the detection of myocardial infarctions and arrhythmias.[9] The objective of this research was to evaluate the specificity in guiding clinical decisions regarding STEMI and NSTEMI in CCUs and CICUs setups by comparing algorithmic interpretation of Spandan smartphone-based 12 lead ECG, developed by Sunfox Technologies Private Limited, Dehradun, Uttarakhand, India with diagnoses made by cardiologists using the 12-lead gold standard machine. The study also included a comprehensive comparative analysis of key diagnostic metrics, including Specificity, Sensitivity, Negative Predictive Value, Positive Predictive Value, Accuracy, Precision, F-score, MCC value, and likelihood ratios for both Spandan ECG and Gold Standard ECG reports.

Methods

Study Design

This cross-sectional, single-blinded, retrospective study was conducted from November 7, 2022, to

Figure 1. Spandan Pro ECG Device.

Table 2. Distribution of the severity of disease in the subjects with target conditions.

Variables	Number	Percentage (%)
Anteroseptal MI	6	10.71%
Anterior wall MI	10	17.85%
Inferolateral MI	2	3.57%
Inferior wall MI	1	1.78%
Antero apical MI	1	1.78%
Ischemia	37	66.07%
LBBB	4	7.14%
RBBB	1	1.78%
ST-T Changes	15	26.78%
J-point Elevation	1	1.78%

December 15, 2022. Reference data from the 12-lead gold standard machine were previously recorded from subjects during their admission to the Cardiac Care Unit (CCU) and Cardiac Intensive Care Unit (CICU), while ECG data from the smartphone device were obtained subsequently. Cardiologist diagnosis were recorded only for ECG reports generated by the 12-lead gold standard ECG machine.

Participants

A cohort of 62 patients, aged over 20 years, presenting with symptoms of chest pain, palpitations, shortness of breath, and pre-existing coronary artery disease (CAD), were included in this study. Patients were recruited from the CCU and CICU of Shri Mahant Indiresh Hospital at Dehradun, Uttarakhand, India, based on convenience and after obtaining written informed consent from each participant. Patients with loose skin were excluded from the study, as were ECG reports exhibiting baseline wandering or indications of only arrhythmia. Additionally, individuals who declined to participate were excluded.

Test Methods

Comprehensive demographic information and detailed medical histories of study participants were recorded in Case Report Forms (CRFs) according to rigorous research protocols. ECGs were obtained for each participant, initially using the 12-lead Gold Standard ECG machine, followed by the Spandan smartphone ECG device. The Mason-Likar placement system was employed for recording ECGs from the smartphone ECG device, while the Goldberger ECG system was used for ECGs from the gold standard machine.

Both sets of 12-lead ECG reports were forwarded to cardiologists for diagnostic evaluation. Cardiologists assessed the reports according to specific criteria for diagnosing ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). The physician's diagnosis was considered the standard evaluation of the specificity of the smartphone ECG device, as its algorithmic outcomes should correlate with clinical diagnosis. Cardiologists were blinded to computer-generated interpretations of both reports to mitigate any bias in diagnosis. ECGs with abnormal outcomes of STEMI and NSTEMI were considered positive, while normal reports were considered negative, with a similar rationale applied to the 12-lead gold standard ECG reports.

Analysis

To analyze the accuracy of the smartphone ECG device, algorithmically generated interpretations were systematically compared with interpretations provided by cardiologists for the 12-lead gold standard ECG reports. Data were compiled and organized within a cloud-based server, while scanned CRFs were securely archived for comprehensive data management. Fixed effect models were employed for the analysis, which involved a comprehensive examination and comparison of ECG reports and their key diagnostic parameters for STEMI and NSTEMI. The parameters analyzed included ST elevations, ST depression, and T wave inversion, categorized by anatomical regions such as the anterior, lateral wall, septal wall, and inferior wall. Data was meticulously evaluated using spreadsheets to calculate diagnostic metrics including true positive, true negative, false positive, false negative, sensitivity,

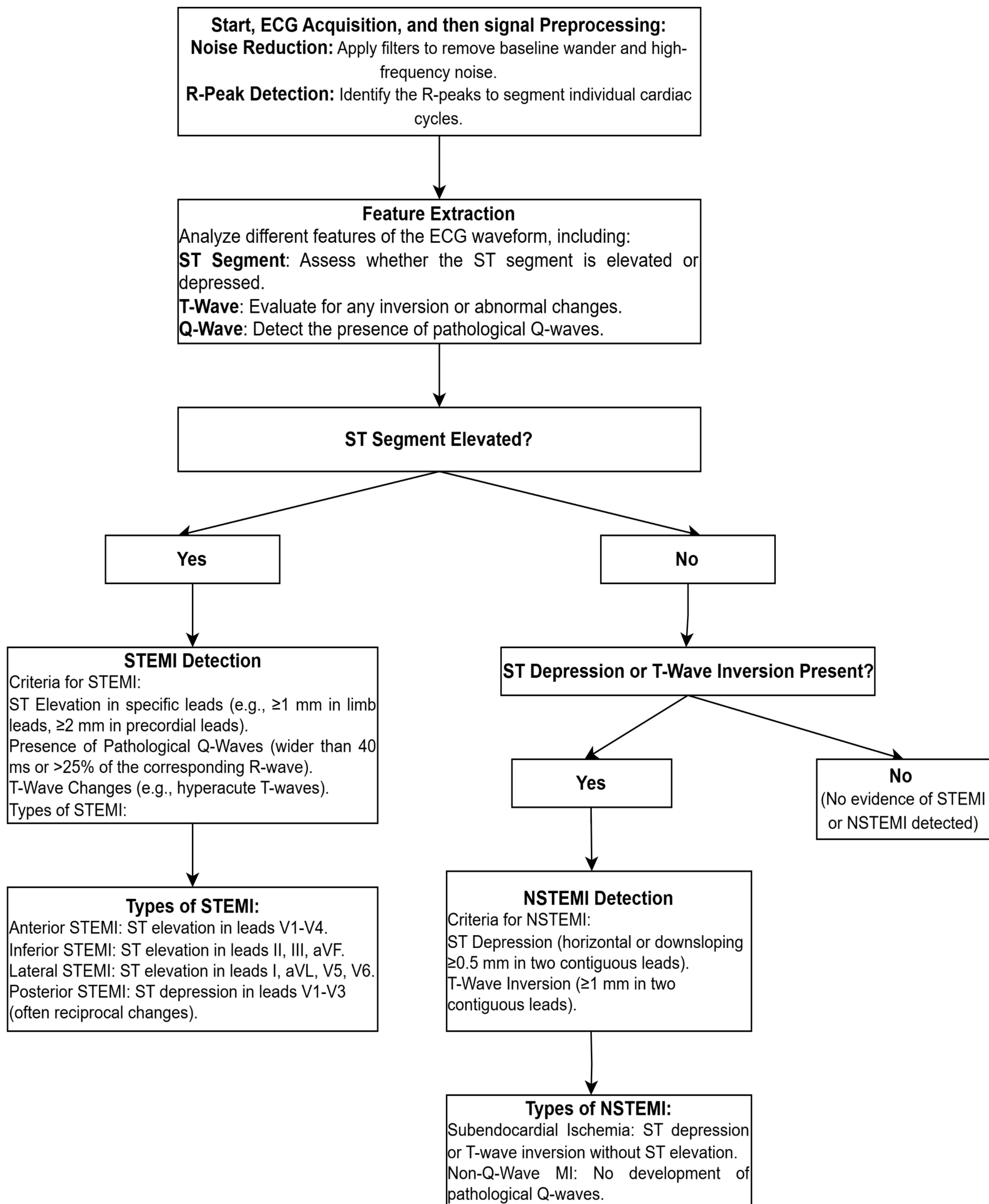

Figure 2. Algorithm of the Device

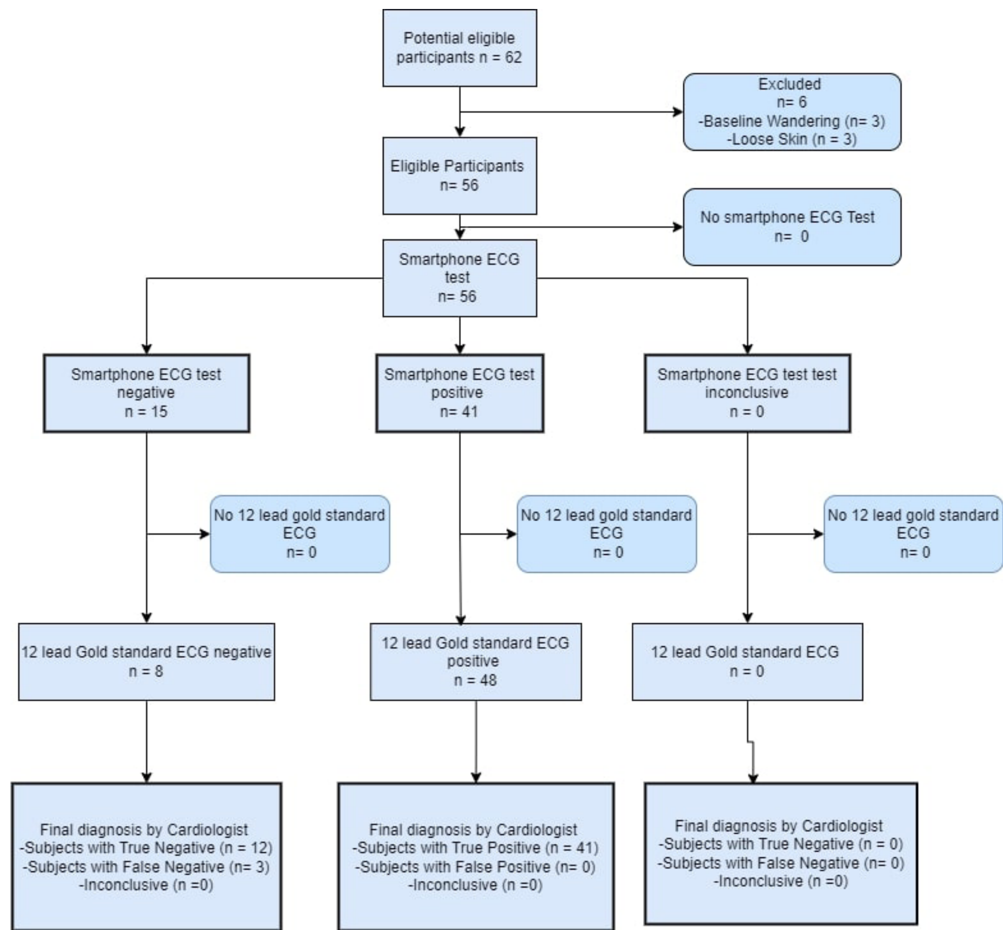

Figure 3. STARD Flow Diagram of the Study: Illustrates participant enrollment, .

specificity, negative predictive value (NPV), positive predictive value (PPV), precision, accuracy, F-score, and Matthew's correlation coefficient (MCC). Statistical evaluations also included a t-test and heterogeneity analysis. Furthermore, likelihood ratios (positive and negative) and 95% confidence intervals for sensitivity, specificity, PPV, and NPV were calculated to assess diagnostic accuracy comprehensively.

Guide for Using the Spandan Pro ECG Device

To perform the ECG recording, the Spandan Pro ECG device was connected to a smartphone to ensure a secure and stable connection. Proper electrode placement was critical for accurate signal acquisition. Following the Goldberg lead placement system, the RA and LA electrodes were positioned on the right and left forearms or wrists, while LL/F and RL/N electrodes were placed on the left and right legs, respectively. Chest electrodes were positioned as follows: C1 (red) at the 4th intercostal space along the right sternum margin, C2 (yellow) at the same level on the left sternum margin, C3 (green) midway between C2 and C4, C4 (brown) at the 5th intercostal space along the mid-clavicular line, C5 (black) at the 5th intercostal space midway between C4 and C6, and C6 (purple) at the 5th intercostal space at the mid-axillary line.

Once the electrodes were securely placed, the test was initiated using the smartphone application, ensuring the patient remained still during the procedure. The generated ECG report was subsequently reviewed for clinical interpretation. In this clinical trial, the Goldberg

Table 3. The decision-making for the accuracy matrix of Spandan ECG and Gold Standard 12 Lead ECG.

Cardiologist Diagnosis	Spandan /Gold standard ECG Interpretation	Accuracy Matrix
Abnormal	Abnormal	True
Normal	Normal	True
Normal	Abnormal	False
Abnormal	Normal	False
Non cases	STEMI/ NSTEMI	Positive
STEMI/ NSTEMI	STEMI/ NSTEMI	Positive
STEMI/ NSTEMI	Non cases	Negative
Non cases	Non cases	Negative
ST-T Changes	15	26.78%
J-point Elevation	1	1.78%

system was employed for electrode placement, and the algorithm utilized by the device, as outlined in Figure 2, was applied for analysis.

Results

This study utilized data from a cohort of 62 patients presenting with both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) to evaluate the diagnostic efficacy of the Spandan smartphone-based 12-lead ECG device. Table 1 presents an overview of the baseline characteristics considered during the ECG assessments of the 62 study participants, with no adverse events recorded. Among these participants, Spandan successfully detected 56 cases exhibiting a spectrum of cardiac abnormalities, including STEMI, ischemia, left bundle branch block/right bundle branch block (LBBB/RBBB), ST-T changes, and J-point elevation, as outlined in Table 2.

The average time difference between capturing the ECG recording with the 12-lead gold standard machine and the Smartphone-based ECG device was 3 hours, primarily due to ECGs being obtained in the Cardiac Care Unit (CCU) and Cardiac Intensive Care Unit (CICU) during patient triage. Meanwhile, recordings with the smartphone ECG machine were acquired

Table 4. Confusion Matrix of ECG Interpretation of Gold standard and Spandan 12 lead ECG.

Parameter	Spandan 12 Lead ECG Interpretation compared to Cardiologist interpretation	Gold Standard ECG Interpretation compared to Cardiologist interpretation
True Positive	41	39
True Negative	12	3
False Positive	0	9
False Negative	3	5

while the patient was admitted to the CCU and CICU. Consequently, a comparative analysis of ECG outcomes related to interpretations by cardiologists is illustrated in Figure 3. Interpretations by cardiologists for gold standard ECG reports that did not align with these findings, particularly those interpreted as normal or exhibiting baseline wandering, or presenting with arrhythmias without any ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI), were excluded from the study. The cardiologist's clinical interpretation confirmed the presence of inferolateral myocardial infarction (MI) and ischemia in the patient, thereby highlighting the potential diagnostic utility of the Spandan ECG device, as depicted in Figure 4 for the 12-lead gold standard ECG and Figure 5 for the Smartphone ECG device.

The evaluation process involved a meticulous comparison between computer-generated interpretations of both the Spandan-derived 12-lead ECG report and the Gold Standard 12-lead ECG report, juxtaposed against the clinical interpretation provided by the investigator.

This comparison was conducted within predefined boundary standards, resulting in the classification of cases into four distinct categories. True positive cases were instances where both computer-generated interpretations and the clinical investigator's interpretation aligned, confirming the presence of detected STEMI/NSTEMI. Cases were considered true negative if both interpretations concurred by correctly indicating the absence of STEMI/NSTEMI under scrutiny. False positive cases comprised computer-generated interpretations suggesting the presence of

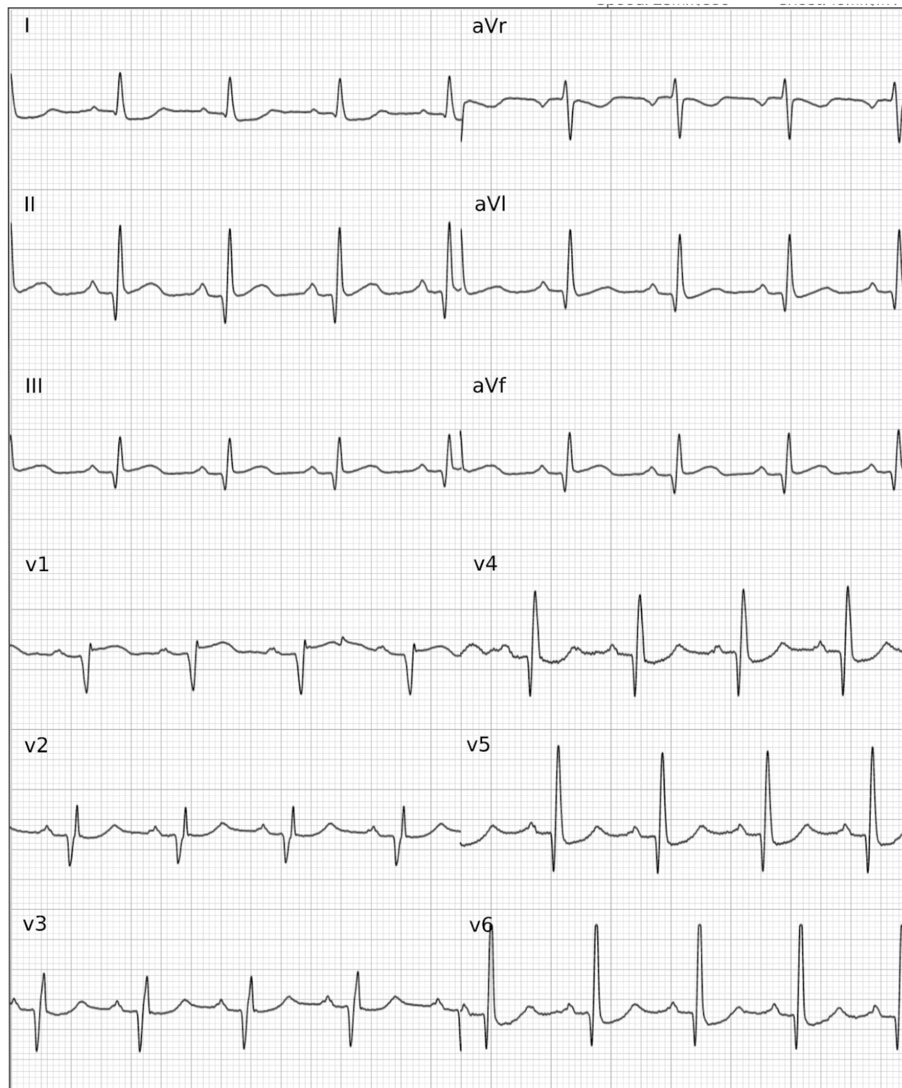

Figure 4. Spandan ECG report of a patient.

STEMI/NSTEMI, but contradicted by the clinical investigator's assessment, resulting in an erroneous positive classification. Conversely, false negative cases occurred when computer-generated interpretations failed to identify STEMI/NSTEMI clinically confirmed by the investigator, leading to misclassification as negative, as outlined in Table 3.

In this analysis of 56 cases, the smartphone-based 12-lead ECG and the gold standard ECG demonstrated comparable diagnostic performance. Both methods correctly identified true positives, true negatives, false positives, and false negatives, as detailed in Table 4.

The validation parameters of the Spandan smartphone ECG device and the gold standard ECG machine are presented in Table 5.

The study demonstrates an F-score of 0.96 for the smartphone-based ECG machine, with a positive likelihood ratio (PLR) of 0.93 and a negative likelihood ratio (NLR) of 0.07. Similarly, the Gold Standard ECG machine demonstrated an F-score of 0.84, indicating a balanced performance in terms of precision and recall. The positive likelihood ratio (PLR) of 1.17 suggests a modest increase in the probability of correctly identifying STEMI/NSTEMI cases when the test is positive. Conversely, the negative likelihood ratio (NLR) of 0.48 reflects a moderate decrease in the probability of ruling

Table 5. Validation parameters of Spandan smartphone ECG and Gold Standard ECG.

Validation Parameter	Spandan 12 Lead ECG	Gold Standard ECG
Specificity	100%	25%
Sensitivity	93%	88%
NPV	80%	37%
PPV	100%	81%
Accuracy	94%	75%
Precision	100%	81%

out STEMI/NSTEMI when the test result is negative. These metrics underscore the diagnostic capabilities of the Gold Standard ECG machine while providing a basis for comparison with alternative methods, such as the Spandan Smartphone ECG. A 95% confidence interval (CI), the true sensitivity of the Smartphone ECG falls within the range of 0.88 to 0.98. Similarly, for the Gold Standard ECG machine, the sensitivity range of 0.83 to 0.93 implies that the equivalent interval lies within the range with the same level of confidence.

The 95% confidence interval for specificity and positive predictive value (PPV) was 1 for the smartphone-based ECG, while for the Gold Standard Machine, these values were between -0.22 to 0.72 and 0.71 to 0.90, respectively. The confidence interval of negative predictive value (NPV) for Smartphone ECG was between 0.2 to 1.4, whereas for the Gold Standard machine, it lies between 0.1 to 0.64.

Additionally, the results indicate that the Smartphone 12-lead ECG yielded Matthew's correlation coefficient (MCC) value of 0.86, while the Gold Standard 12-lead ECG produced an MCC value of 0.16. This substantial discrepancy in MCC values suggests that the diagnostic performance of Spandan significantly outperformed the Gold Standard ECG, reinforcing the robustness of Smartphone ECG's diagnostic capabilities.

The p-value of 0.002 observed in the comparison of the gold standard versus cardiologist interpretation and Spandan versus cardiologist interpretation for detecting STEMI/NSTEMI indicates a statistically significant difference between these diagnostic approaches. Additionally, the high heterogeneity reflected in the I^2 statistic (99.68% for specificity and 95.4% for sensitivity) highlights substantial variability across the studies included in the analysis. This suggests that the differences in sensitivity and specificity outcomes may be influenced by diverse study methodologies, population characteristics, or diagnostic protocols, emphasizing the need for standardized evaluation across varied clinical settings. A detailed comparison of the Spandan Smartphone ECG's diagnostic performance with outcomes from prior research is presented in Table 6.

Table 6. Comparison of the Spandan Smartphone ECG outcomes to the previous studies.

Study Name	Muller et al. Study for Smartphone ECG	Towhari et al study for Arrhythmia	Spandan ECG
Sensitivity (%)	88	97.3	100%
Specificity (%)	69	99.6	93%
PPV (%)	83	NA	80%
NPV (%)	NA	NA	100%

Discussion

The primary aim of this study was to validate the effectiveness of the Spandan smartphone-based ECG device in making crucial decisions related to ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). Compared to the Gold Standard ECG, the Smartphone ECG device demonstrated a notably higher level of accuracy and precision. This finding suggests that Smartphone-based 12-lead ECG could play a crucial role in setups like Intensive Care Units (ICUs) and Cardiac Intensive Care Units (CICUs) where the gold standard ECG has limitations in providing digitized ECG reports during the physical absence of the cardiologist. Previous studies have shown that handheld ECG and portable ECG devices are good alternatives for cardiac care monitoring in home settings, primary healthcare facilities, and rural areas. In addition to early detection of cardiac abnormalities like arrhythmias, Smartphone-based 12-lead ECG machines can also facilitate early discharge of patients and provide timely diagnosis even when the cardiologist is unavailable in the CCU and CICU.

Muhlestein et al. in 2019 assessed the accuracy of diagnosing STEMI by combining consecutive single-lead smartphone ECGs to create a simulated 12-lead

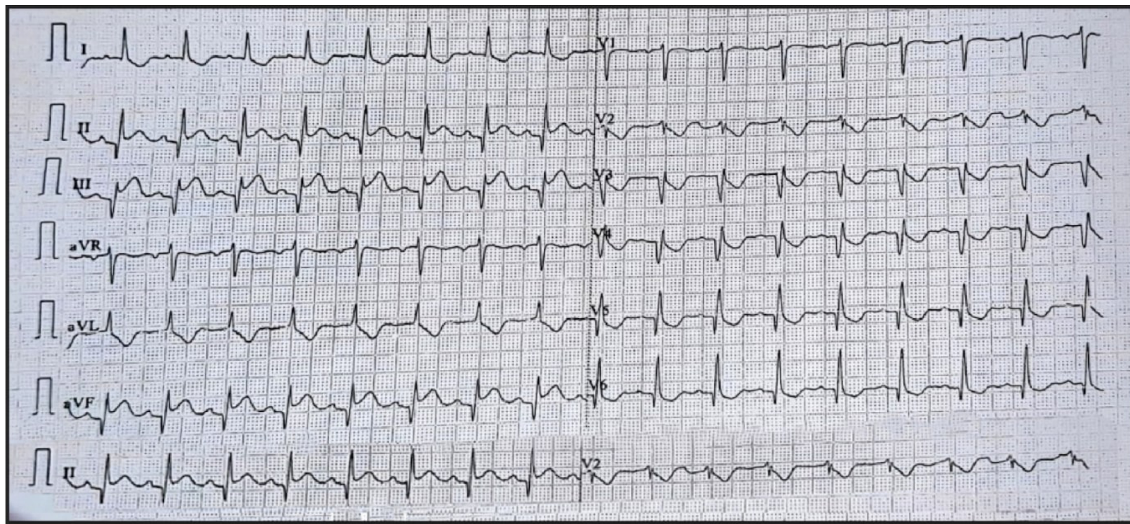

Figure 5. Gold Standard ECG report of a patient.

ECG, indicating equivalence to the 12-lead gold standard ECG in detecting STEMI effectively. This innovative approach not only broadens the possibilities for quicker and more comprehensive diagnosis but also has the potential to enhance STEMI treatment outcomes by facilitating early intervention.

Similarly, Muller et al. in 2008 showed that out-of-hospital ECG had an 88% sensitivity, 69% specificity, 77% positive predictive value, and 83% negative predictive value. Towhari et al. in 2019 compared the diagnostic accuracy of smartphone ECG recorders with that of standard 12-lead ECG in hospital settings. Analysis revealed diagnostic metrics of smartphone ECG recorders similar to standard 12-lead ECG rhythm, including sensitivity (97.3% vs. 98%) and specificity (99.6% vs. 99.6%). However, their study was limited to arrhythmias, whereas the current study included STEMI and NSTEMI to further evaluate the diagnostic accuracy of smartphone electrocardiogram devices in critical patients. On comparing these findings with the Spandan smartphone ECG, accuracy parameters showed higher values for the Spandan ECG.

Although these findings were analyzed for a small sample size, this research opens the door for a large-scale study. The smartphone ECG machine used in this study shows extreme sensitivity in the ECG traces, signifying that these devices can be used in the screening of vulnerable STEMIs and NSTEMIs. The algorithms of computer interpretation are 24% more specific compared to the study conducted by Muller et al. Additionally, the Smartphone ECG in this study predicted no false positive values.

With the limitation that the research was conducted on a small number of participants within a single healthcare facility, the majority of whom were males, the generalizability of the findings to a broader and more diverse population may be restricted. Additionally, a single device was employed to carry out all tests. While this was done under the guidance of well-trained trial assistants, it's crucial to recognize that the accuracy of recorded ECG tracings may vary when utilized by individuals without specialized training, especially if they do not follow proper usage instructions.

The use of mobile devices by healthcare professionals is transforming clinical practice. Numerous medical software applications can now assist with tasks ranging from information and time management to clinical decision-making at the point of care. Mobile devices and applications offer a wide array of advantages to healthcare professionals, including heightened accessibility to point-of-care tools. This increased accessibility has been shown to play a pivotal role in enhancing clinical decision-making processes, ultimately resulting in improved patient outcomes. In essence, mobile technology empowers healthcare professionals by equipping them with an arsenal of tools and information that can significantly impact the quality of care they provide and, by extension, the well-being of their patients.

Nonetheless, further research is warranted to

explore smartphone-based ECG potential in detecting a broader spectrum of its capability to make percutaneous coronary intervention (PCI) related decisions and its correlation to 2D and 3D imaging techniques like echocardiography and angiography.

Conclusion

The Spandan ECG, a smartphone-based device, demonstrates remarkable efficacy in the detection of ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), making it a promising solution for Cardiac Care Units (CCUs) and Cardiac Intensive Care Units (CICUs) settings for monitoring purposes. The findings of this observational study emphasize smartphone-based ECG's diagnostic capabilities for specifically detecting STEMI and NSTEMI in critical patients, particularly in terms of specificity (100%) and accuracy (93%). These results highlight that the digital health device has the potential to aid cardiologists in making timely diagnoses and initiating treatment, ultimately contributing to the reduction of mortality rates associated with cardiovascular conditions.

List of Abbreviations

CCU	Cardiac Care Unit
CICU	Cardiac Intensive Care Unit
ECG	Electrocardiogram
ICU	Intensive Care Unit
MCC	Matthew's correlation coefficient
MI	Myocardial Infarction
NLR	Negative Likelihood Ratio
NPV	Negative Predictive Value
NSTEMI	Non-ST-segment elevation myocardial infarction
PCI	Percutaneous Coronary Intervention
PLR	Positive Likelihood Ratio
PPV	Positive Predictive Value
SST	T-segment elevation myocardial infarction

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Case Report

Non–surgical Intervention for Palliative Treatment in Late–presentation Tetralogy of Fallot (TOF): Is There Any Hope?

Indah Pratiwi Siregar,[1] Radityo Prakoso.[1]

Abstract

Background: Late congenital heart disease (CHD) in patients with tetralogy of Fallot (TOF). Due to the variable severity of defects in patients with TOF, late presentation of CHD may only be discovered beyond the neonatal period. Chronic polycythemia from TOF may increase the risk of hemorrhaging during surgery and patients with untreated TOF risk developing CHD-related pulmonary hypertension. Non-surgical transcatheter palliation in patients with TOF may be applied; however, studies regarding the efficacy and safety of the method remained very scarce. Therefore, we report two cases of late-presenting TOF treated with non-surgical transcatheter palliation due to high perioperative risks for surgical repair of the defects.

Case Illustration: A 41-year-old (Case 1) and 19-year-old man (Case 2) were admitted to the emergency room due to a chief complaint of dyspnea and severe headache with a previous history of hypoxic spells, respectively. Physical findings showed signs of cardiomegaly and right ventricular hypertrophy. Echocardiography confirmed TOF for both cases. Due to high perioperative risks for surgical repair, non-surgical palliation for both cases was performed, with Right Ventricular Outflow Tract (RVOT) stenting for case 1 and Balloon Pulmonary Valvuloplasty (BPV) for case 2. Both cases showed systolic function and functional capacity improvement after both interventions.

Conclusion: Non-surgical transcatheter palliation is the preferred treatment approach for late-presentation TOF that pose major comorbidities such as hypercyanotic spell and myocardial dysfunction which are not amenable to surgery. Although PA size after palliation had not been evaluated further yet, Improvement of systolic function and functional capacity denoted the benefit of initial palliation. Thus, non-surgical transcatheter palliation as a bridging procedure before complete surgical repair in late-presentation TOF might be a promising option.

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Keywords: *Complications, congenital heart disease, palliative, Tetralogy of Fallot.*

[1] Department of Cardiology and Vascular Medicine, Division of Pediatric Cardiology and Congenital Heart Disease, Faculty of Medicine, Universitas Indonesia.

Correspondence:
Indah Pratiwi Siregar,
Department of Cardiology and Vascular Medicine, Division of Pediatric Cardiology and Congenital Heart Disease, Faculty of Medicine, Universitas Indonesia.
Email : pratiwwwi@gmail.com.

Introduction

Late Congenital Heart Disease (CHD) refers to late presentation in the natural history of the specific cardiac defect, with consequent transient or irreversible hemodynamic and pathologic alterations that would impact the medical and surgical approach, risk, and outcome.[1,2]

Tetralogy of Fallot (TOF) is one of the most common late cyanotic CHD. TOF occurs in approximately 1 in 3600 live births and accounts for 3.5% of infants born with congenital heart disease.[2] Chronic cyanosis in the setting of unoperated tetralogy of Fallot can lead to polycythemia with or without disseminated intravascular coagulopathy, hepatic or renal dysfunction, or stroke. In low- and middle-income countries, however, patients with tetralogy of Fallot commonly present for the first time during childhood, adolescence, or even late adulthood. Some would be natural survivors of the so-called "good anatomy tetralogy of Fallot" with minimal cyanosis and therefore manifest limited consequences of chronic cyanosis. Most patients, however, are markedly cyanotic and may manifest the deleterious sequelae of chronic polycythemia with hyper-viscosity and varying degrees of consumptive coagulopathy.[3] Furthermore, Chronic polycythemia increases the risk of postoperative bleeding from surgical sites, as well as internal organs. CHD-related pulmonary hypertension has been extensively reviewed elsewhere. The incidence of postoperative pulmonary hypertension is much higher in late-presenting CHD.[1,2,4–6]

Uncorrected Tetralogy of Fallot with major comorbidities is significantly limited for definitive complete repair since it could lead to polycythemia with or without disseminated intravascular coagulopathy, hepatic or renal dysfunction, or stroke.[3,7] Traditionally, palliative options such as a surgical systemic to pulmonary shunt (Blalock-Taussig or BT shunt) are frequently employed as bridging procedures before definitive complete repair. Late-presentation Tetralogy of Fallot (TOF) poses major comorbidities that increase the risk of surgery.[1,2] Procedure due to high risk for surgery.

Case Presentation

Case 1

A 41-year-old man was admitted to our hospital with a complaint of breathlessness at rest three days ago accompanied by bilateral leg edema. He had a history of having phlebotomy about 3 times. He knew that he had cardiac disease in the last 6 months. He was also visibly fatigued and experiencing dyspnea without any loss of consciousness or seizure. He denied having a history of breathlessness or bluish-lips discoloration since birth, he also did not have a history of stunted growth and difficulty in feeding. He was born spontaneously, at term, with a birth weight of 3300 g. No family history with the same symptoms were reported.

On physical examination, the patient was lethargic and looked very ill. Body weight of 55 kilograms, body height of 160 cm, blood pressure was 131/84 mmHg, heart rate 96 bpm, respiratory rate 20 x/min, and body temperature was 36.7 C. Peripheral oxygen saturation was 65%. Jugular Venous Pressure (JVP) was distended (5+4 cm H2O). An auscultatory examination showed normal first heart sound, single not attenuated second heart sound was found with ejection systolic murmur grade 3/6 in the upper left sternal border. Hepatic enlargement palpated 2 cm below arcus costae. Both extremities showed clubbing fingers and cyanotic. Electrocardiography showed sinus rhythm and right axis deviation (RAD) with Right Ventricular Hypertrophy (RVH).

Electrocardiography examination at admission showed sinus rhythm, QRS rate 75 x/m, QRS axis +124, QRS duration 80 ms, Abrupt R V1-V2, Right Axis Deviation (RAD), Right Ventricular Hypertrophy (RVH). Chest Xray (C-XR) 3 months before admission showed heart enlargement with cardiothoracic ratio of 66%, reduced pulmonary segment, flatten cardiac waist, upward apex, which showed a boot shaped heart and oligemic pulmonary vascular pattern without pulmonary infiltrates A 2D echocardiography examination was performed to evaluate the LV and RV function. It showed normal LV size with good LV systolic function (LVEF 71%), dilated and right ventricular hypertrophy with normal RV systolic function (TAPSE 18 mm), and moderate to severe tricuspid regurgitation (TR V max 5,3 m/s) (Figure 4. A-D). On the 2D echocardiography,

50% overriding aorta accompanied with antero-cephalad deviated septum which caused infundibular and valvar pulmonary stenosis, subaortic VSD with diameter 22 mm, L to R shunt with good LV systolic function (LVEF 71%), dilated and right ventricular hypertrophy with normal RV systolic function (TAPSE 18 mm).

A 3D echocardiography examination was performed. It showed that LVEF was 59% and RVEF was 49% Laboratory examination showed polycythemia with elevated. Hemoglobin and Hematocrit level Hemoglobin 20.2 g/dl, Hematocrit 69%). He was then diagnosed with TOF.

Cardiac multi-slice computed tomography (MSCT) was performed to measure pulmonary artery size. The scan showed a McGoon Ratio of 1.7, PA half size 14 mm, Bilateral SVCs, Collaterals from the Descending Aorta, and Normal coronary artery. The patient was planned for RVOT stenting with no. 10 mm x 56 mm with balloon pre-dilatation using no. 7,0 mm x 80 mm. The stent was placed in RVOT with a good result. Angiography was performed to visualize the RVOT obstruction due to Infundibular Pulmonary Stenosis. Before RVOT stenting, Pre- dilatation with Balloon no. 7,0 mm x 80 mm was performed followed by stent placement no. 10 mm x 56 mm at RVOT. After RVOT stenting, we performed 3D TTE to evaluate the LV function and RV function. It showed LV systolic function LVEF 67% by 3D echocardiography, dilated and hypertrophy right ventricle, RVEF 42%, RV FAC 36%, RV free wall GLS -11,3%. There is a stent attached to RVOT with a proximal stent protruding to the RV inflow area without disturbing tricuspid closure. RV-PA gradient 70 mmHg, mild tricuspid regurgitation, TVG 100 mmHg.

Case Illustration 2

A 19-year-old boy came to the National Cardiovascular Centre Harapan Kita with a chief complaint of severe headache lasting for a day. Severe headache accompanied by a history of three times episodes of hypoxic spell in the last 1 year. The patient also felt easily fatigued and breathless after doing mild activities. The patient also had a history of bluish discoloration on lips and tip of nails fingers and toes in the last 2 years. Patients had a history of repeated phlebotomy about 7 times a year. No prior history of repeated cough or fever, his parents mentioned a history of cyanotic spell at 8 months of age. He was born spontaneously, assisted by a midwife, with no history of blue appearance after birth, birthweight of 4200 grams, and no history of familial congenital heart disease.

On physical examination, the patient was fully conscious but looked severely ill. Body weight of 59 kilograms, body height of 170 cm, blood pressure was 178/112 mmHg, heart rate 96 bpm, respiratory rate 20 x/min, and body temperature was 36.7 C. Peripheral oxygen saturation was 60%. Jugular Venous Pressure (JVP) was not distended, Auscultatory examination found normal first heart sound, the single not attenuated second heart sound with ejection systolic murmur grade 3/6 in the upper left sternal border. Both extremities showed clubbing fingers and cyanotic. Electrocardiography examination showed sinus rhythm with Right axis deviation (RAD) and Right Ventricular Hypertrophy (RVH).

The ECG 1 year before BPV showed sinus rhythm, QRS rate 113 x/m, Abrupt R V1-V2 with Right axis deviation (RAD) and Right Ventricular Hypertrophy (RVH). Chest x-ray 4 days before BPV showed heart enlargement with cardiothoracic ratio 60%, flatten cardiac waist, slightly upward apex and oligemic pulmonary vascular pattern and no pulmonary infiltrates seen. The 2D echocardiography showed normal LV size with reduced LV systolic function (LVEF 49%) and reduced RV systolic function (TAPSE 11 mm) with 50% Overriding aorta accompanied with antero-cephalad deviated septum which caused severe valvar pulmonary stenosis (PS), subaortic VSD with diameter 21 mm, L to R shunt. The patient was planned to have a right heart catheterization and was scheduled for 22nd October 2021. However, before RHC was performed, it was found that peripheral saturation was 53% and TEE evaluation pre-RHC found Tetralogy of Fallot, subaortic VSD with valvar severe Pulmonary Stenosis then it was decided to do Balloon Pulmonary Valvuloplasty (BPV). The balloon was successfully dilated with an improvement of RV-PA gradient from 77 mmHg to 50 mmHg and peripheral saturation was significantly improved from 53% to 90% while aortic saturation was significantly improved from 76% to 94%.

Angiography was performed to visualize the

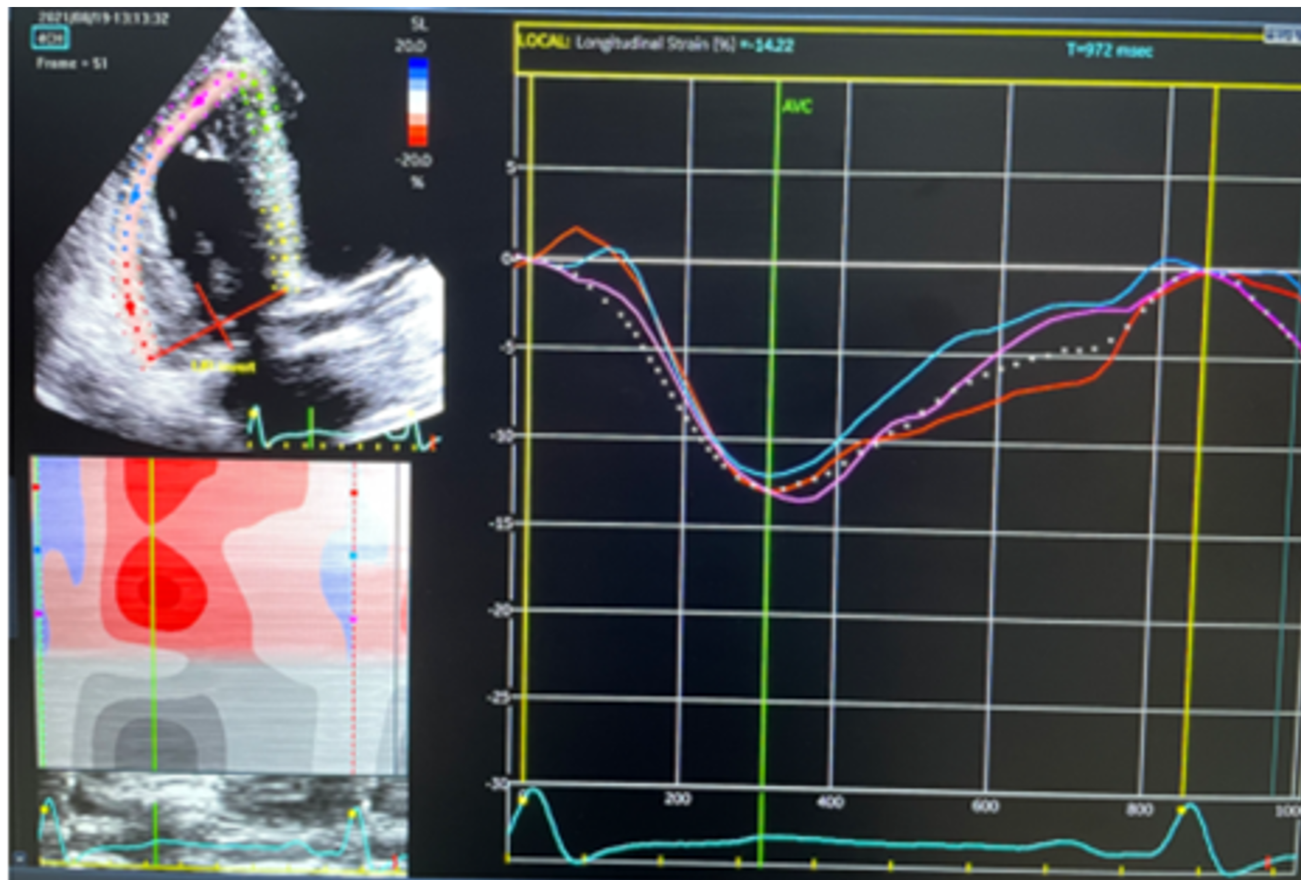

Figure 1. Speckle tracking echocardiography to assess RV-free wall GLS after RVOT stenting.

RVOT obstruction due to severe valvar Pulmonary Stenosis. BPV was performed by dilating the Balloon 18 mm x 3.0 mm x 110 cm RV-PA until the balloon waist disappeared. After BPV, we performed 3D TTE and speckle tracking echocardiography to evaluate LV function and RV function. It showed RV Free Wall GLS -17,8% and LV GLS -14,7% after BPV.

Discussion

Non-surgical palliation approach in late presentation TOF

Twenty-five percent of infants with severe obstruction not treated surgically will die within the first year.[1] If Left untreated, about 40% of TOF patients will die by age 3 years, 70% by age 10 years, and 95% by age 40 years. After the first year, the risk is constant until age 25 years, but then it increases.[1] The severity of RVOTO dominates clinical presentation. Moderate RVOTO gives rise to a systolic murmur in an asymptomatic child. Cyanosis may develop between 6–8 months as infundibular stenosis increases, producing a right to left shunt. The presentation may also be with a hypercyanotic attack from total obstruction of the infundibular.[6] Major comorbidities found in TOF such as severe cyanotic condition, small pulmonary arteries, atrioventricular Septal Defect (AVSD), or complex defects are considered to be high preoperative risk for surgical repair.[6,7] Chronic hypoxia in late presentation TOF is a strong risk factor for myocardial dysfunction. Traditionally, surgical systemic to pulmonary shunt (Blalock-Taussig or BT shunt) is frequently employed as bridging procedures for patients who are not ideal for complete surgical repair. With the advancement of technology, non-surgical palliation was intended to be a salvage procedure for late presentation that poses high-

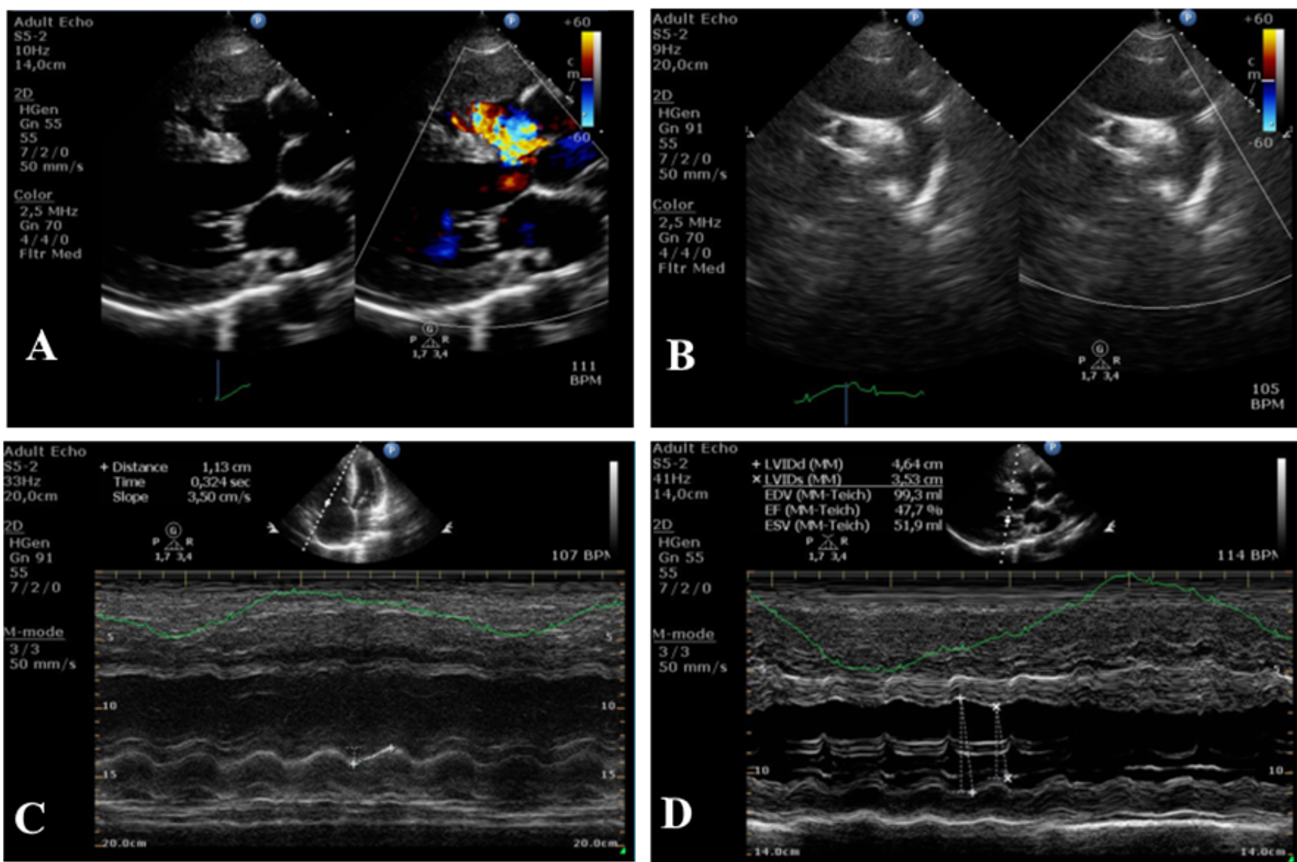

Figure 2. (A). Echocardiography 2D before BPV showed 50% Overriding aorta accompanied by anterocephalad deviated septum which caused (B) severe valvar pulmonary stenosis (PS), subaortic VSD with diameter 21 mm, L to R shunt (C) reduced LV systolic function (LVEF 71%), (D). dilated and right ventricular hypertrophy with reduced RV systolic function (TAPSE 18 mm).

risk conditions for surgery.[8,9] Recent options such as Right Ventricular Outflow Tract (RVOT) stenting and Balloon Pulmonary Valvulotomy (BPV) had already been known as non-surgical palliation.

In our case, RVOT stenting was performed in case 1 due to a hypercyanotic spell with myocardial dysfunction due to chronic hypoxia. Due to infundibular pulmonary stenosis, RVOT stenting is preferred over other approaches. BPV was performed in case 2 due to a hypercyanotic spell since it had pulmonary valvular stenosis. BPV is preferred over other approach in pulmonary valvular stenosis cases.[1,6]

Surgical Primary Repair following Initial Palliation

Trend had been increasingly toward primary repair ever since Castaneda and Jonas demonstrated in the 1980s that excellent outcomes could be achieved in early infancy. Numerous studies demonstrated that primary repair of ToF between the ages of 3-9 months has become the standard of care. However, higher-risk patients in whom staged repair may still be indicated could be divided into: (i) neonates/small infants with small pulmonary arteries (PAs) and (ii) complex anatomical variants (such as Fallot/Atrioventricular Septal Defect [AVSD] or major non-cardiac conditions) where single-stage repair may carry higher risk or there may be benefit from planned delay.

Concern towards primary surgical repair after RVOT stenting had been increasing. Barron, et al showed low procedural-related mortality in surgical repair following RVOT stenting. RVOT stenting seems a safe alternative to systemic-to-pulmonary shunting to achieve improved

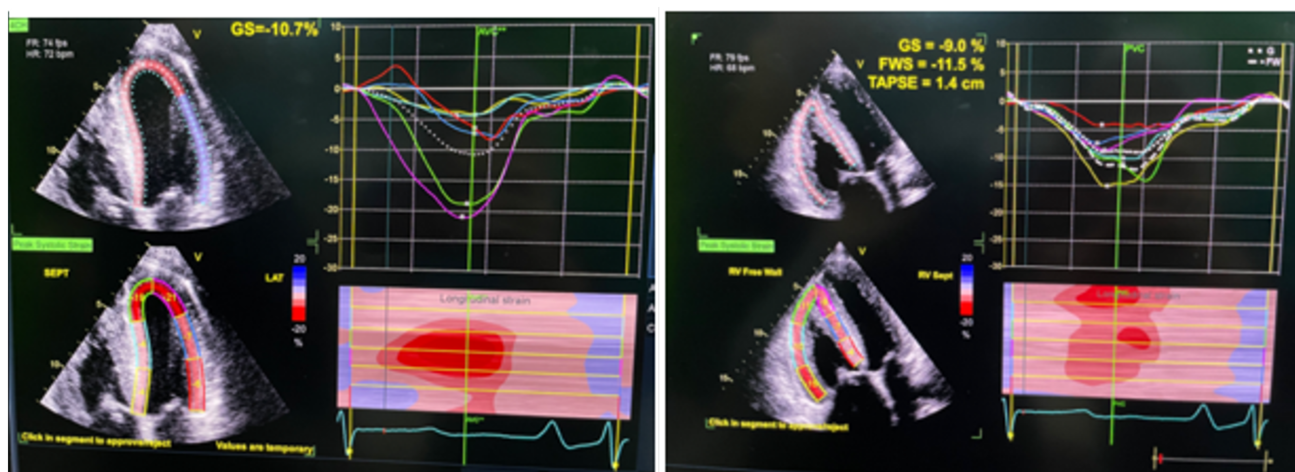

Figure 3. Speckle tracking echocardiography showed RV Free Wall GLS -11,5% (left) and LV GLS -10.7% before BPV (right).

pulmonary blood flow while avoiding low diastolic pressures. The study also demonstrated that PA growth following stenting might create a more suitable substrate for subsequent repair, especially for severe cyanosis and very small-branch PA patients. Previous studies also demonstrated that stent can successfully palliate these patients such that elective repair can be performed with better-sized PAs.[10]

Similar with RVOT stenting, BPV is one of the established initial palliation in treating Tetralogy of Fallot mainly with pulmonary valvular stenosis cases. Some studies have shown that BPV may reduce the need for transannular patching (TAP) in patients with TOF. Some patients may require additional surgery before receiving total correction due to valvular pulmonary restenosis and these patients are at risk of pulmonary regurgitation. However, Geena et.al demonstrated that BPV produces outcomes similar to other palliative procedures and allows for a higher rate of PV annulus growth compared with other modalities, which may alleviate the need for TAP in patients with an initially small PV annulus.

As the previous study aforementioned, both cases will undergo primary complete surgical repair with better pulmonary artery size and a higher rate of PV annulus growth after initial palliation. Both cases should be monitored for pulmonary artery size, ventricular function, and valvular pathology to minimize further complications of surgical primary repair.

RVOT stenting vs BPV

RVOT stenting emerged as a good alternative for BT shunt with acceptable early and long-term outcomes and continues to be an important option in the initial management of cyanotic patients with low birth weight, inadequate pulmonary artery size, or complex anatomy.[9,10] RVOT stenting resulted in improving the pulsatile forward flow of systemic venous blood to the pulmonary artery, improving arterial O2 saturation, as well as improving pulmonary arterial growth. RVOT stenting has become one of the preferred transcatheter palliations with better branch pulmonary arterial growth as compared to modified BT shunts.[11]

While BPV was the earlier interventional palliation, it has limited utility in patients with predominantly infundibular obstruction. Studies demonstrated that balloon dilatation clearly resulted in a rise in pulmonary valve dimensions, with a mean gain of 1.74 standard deviations immediately after dilatation and 2.17 SD before surgical correction. The balloon-to-annulus ratio correlated significantly with the change in pulmonary annulus diameter, with the biggest increase observed with a balloon-to-annulus ratio of 1.5. Balloon pulmonary valvotomy would logically work best when there is predominantly valvar pulmonary stenosis in a patient with an adequately sized pulmonary annulus. Often, in newborns and young infants, the degree of infundibular hypertrophy is less, and hence BPV may yield satisfactory results despite this theoretically multilevel obstruction in Tetralogy of Fallot.

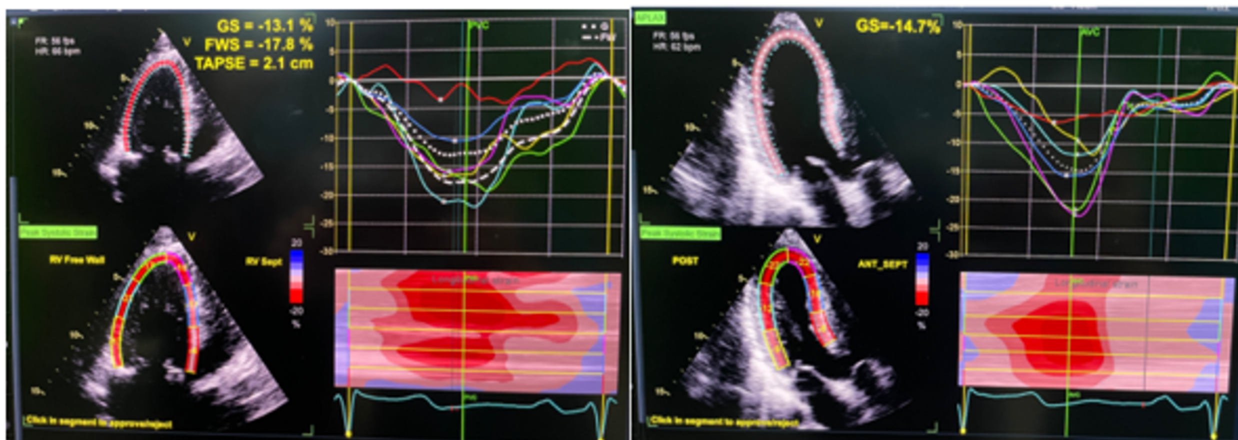

Figure 4. Speckle tracking echocardiography showed RV Free Wall GLS -17,8% after BPV (left) and LV GLS -14,7% after BPV (right).

Unlike BPV, RVOT stenting would address the predominantly infundibular stenosis, and pulmonary annular hypoplasia with higher effectiveness and reliability compared to static balloon dilation.[9] In our case, we did not perform BPV followed by RVOT stenting if echocardiogram and angiograms suggest multilevel RVOT obstruction which would have a suboptimal result with BPV.[13–15] The underlying reasons are highlighted. First, BPV itself may precipitate cyanotic spells and would make the condition become more unstable and higher risk. Second, if we plan to anchor the RVOT stent across the pulmonary annulus, prior BPV could increase the potential risk of stent migration by enlarging the valvar constriction, or forcing the use of an oversized RVOT stent leading to pulmonary overcirculation.

Functional Capacity after non-surgical palliation intervention

The 6-MWT distance predicted cardiovascular events and provided similar prognostic value to treadmill exercise capacity. It was previously reported that decreasing 6-MWT distance was an independent predictor of increasing mortality in patients with left ventricular systolic dysfunction. Although cardiopulmonary exercise testing (CPET) is a gold standard method for assessing exercise capacity, the more commonly used test for assessing LV function is the 6-minute walk test (6-MWT).[18,19]

After palliation, case 1 was able to have the 6-min walk distance in 320 m (3.7 METS) in first trial and 7 days later increasing to 800 m (9.1 METS) meanwhile Case II was able to have the 6-min walk distance in 474 m (5.0 METS) and 7 days later increasing into 1200 m (11.2 METS). Both cases showed improvement in functional capacity in terms of METS after having a non-surgical palliation transcatheter.

Conclusion

Non-surgical transcatheter palliation is the preferred treatment approach for late-presentation TOF that pose major comorbidities such as hypercyanotic spell and myocardial dysfunction which are not amenable to surgery. RVOT stenting is the preferred non-surgical palliation option for predominantly infundibular pulmonary stenosis meanwhile BPV is a safe and effective option for predominantly valvular pulmonary stenosis. Although PA size after initial palliation had not been evaluated further yet, improvement of systolic function and functional capacity denoted the benefit of initial palliation. Thus, non-surgical transcatheter palliation as a bridging procedure before complete surgical repair in late-presentation TOF might be a promising option.

Acknowledgments

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Conflict of Interest

The case report was self-funded; no conflict of interest was reported for both authors.

List of Abbreviations

6-MWT	6-minute walk test
AVSD	Atrioventricular Septal Defect
BPV	Balloon Pulmonary Valvulotomy
CHD	Congenital Heart Disease
CPET	Cardiopulmonary Exercise Testing
PAs	Pulmonary Arteries
PS	Pulmonary Stenosis
RAD	Right axis deviation
RVH	Right Ventricular Hypertrophy
RVOT	Right Ventricular Outflow Tract
TTE	Transthoracic Ehocardiography
TOF	Tetralogy of Fallot
TAP	Transannular Patching

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Case Report

Beneath The Rhythm: Deciphering The Subtle Perforation of The Right Ventricle by a Pacemaker Lead

Kalyan Munde,[1] Mohan Paliwal,[1] Akshat Jain.[2]

[1] Dept. of Cardiology Grant Government Medical College and Sir J.J. Group of Hospitals, Mumbai.
[2] Grant Government Medical College and Sir J.J. Group of Hospitals, Mumbai.

Correspondence:
Kalyan Munde, Dept. of Cardiology Grant Government Medical College and Sir J.J. Group of Hospitals, Mumbai.
Email: kalyanmunde@yahoo.com.

Abstract
Cardiac perforation by the lead of permanent pacemaker implantation (PPM) devices is a critical complication that often occurs within 24 hours after the implantation but can occur later. Here we report a case of 82-year-old female patient with perforation of the right ventricular wall due to RV lead after 3 months of pacemaker implantation, which was managed conservatively.

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Keywords: *Right ventricle perforation, pacemaker lead, permanent pacemaker, conservative management, pericardial effusion, sick sinus syndrome, cardiac device complications.*

Introduction

Cardiac perforation due to a pacemaker or defibrillator lead occurs at a rate of 0.4–2.0%.[1] The incidence of this complication from the time of surgery decreases over time. By convention, a perforation which is detected within the first 24 hours, is classified as acute. If it is detected within 30 days of implantation (between 5 days- 4 weeks), it is referred to as early (sub-acute); and, those detected after 30 days are referred to as late, delayed, or chronic perforation.[1,2] Most perforations manifest within a year but rarely cases have been reported as late as five years following implantation. The critical risk factors for lead perforation are not yet clear. Therefore there are many controversies in the management of lead perforation depending on the symptoms, chronicity, and functional status of the device.

Case Details

An 82-year-old female patient underwent permanent pacemaker implantation at our institute 3 months ago for sick sinus syndrome (tachy-brady syndrome), which caused multiple episodes of syncope before admission. She has shown improved symptoms since the implantation. The pacemaker, which is a Medtronic device, is set in DDDR (Dual-chamber rate-modulated pacing) mode, MRI conditional, with a lower rate of 60 bpm. The details of the settings are mentioned in Table 1.

After being asymptomatic for two and a half months after discharge, however, this time, she presented with complaints of shortness of breath for the last 2 weeks. It was followed by the appearance of a pitting type of pedal oedema in both lower limbs for past 5 days, and orthopnoea for the last 2 days.

On evaluation, the patient presented with biventricular heart failure and volume overload. The pulse rate was 130/min irregular, BP was 144/90 mmHg, oxygen saturation was 88% on room air, and respiratory rate was 24/min. (Figure 1).

ECG was suggestive of atrial fibrillation with fast ventricular rate. Chest x-ray P/A view suggestive of bilateral pleural effusion with cardiomegaly with PPM device, RA, and RV lead in situ. 2D Echocardiography showed moderate pericardial effusion with no e/o RA, RV collapse, or cardiac tamponade with RA lead in place and RV lead in pericardial space with LV and RV dysfunction. (figure 2:A-D).

Table 1. Pacemaker parameters.

Parameters	RA Lead	RV Lead (baseline)	RV lead (current)
Threshold	1.2 V at 0.5 ms	0.5 V at 0.5 ms	2.5 V at 0.4 ms
P/R wave	2.5 mv	11.2 mv	8.2 mv
Impedance	558 ohm	893 ohm	549 ohm

Table 2. Laboratory examinations of pericardial fluid.

Hb: 12.6 gm. / dl.	ESR:25mm/1hr	NT pro BNP:16,345 pg. /ml.
TLC: 7500/ cu.mm	CRP:3.95 mg/L	TSH: 6.76 mIU/L.
Platelet:2.3 lakh/cu.mm	Creatinine: 0.8 mg/dl.	Free T4: 1.28 ng. /dl.

On-device interrogation, we found that the RV lead threshold increased to 2.5 V at 0.4 ms, and the impedance value decreased to 549 ohms (Table 1).

The CECT Thorax revealed a pacemaker with one lead in the right atrium and the other perforating the apex of the right ventricle (5x6 mm) with no signs of any active contrast leak or extravasation into the pericardium. There are bilateral moderate pleural effusion, moderate pericardial effusion, and cardiomegaly with dilated right and left atria, as well as evidence of cardiogenic pulmonary oedema.

Management

After a thorough discussion with the cardiac surgeon and considering the patient's delayed presentation, vital status, advanced age, and frail body habitus, it was decided to manage the patient with medical treatment. This included rate-controlled medication, decongestive therapy, and oxygen support. The patient was continuously monitored for her symptoms and changes in effusion.

Pericardiocentesis was performed 5 days after admission, and 325 ml of haemorrhagic fluid was drained. There were blood clots in the aspirated pericardial fluid and the fluid was hemorrhagic in nature. It was sent to the lab for analysis to rule out

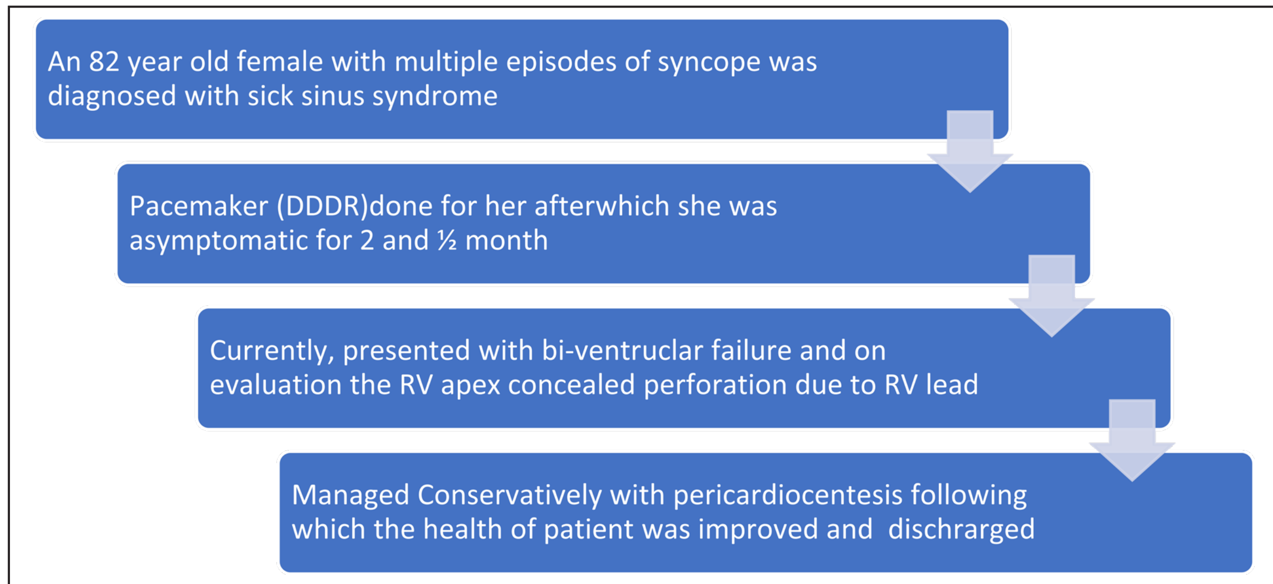

Figure 1. Timeline of the events

the possibility of infection. The analysis revealed that the fluid was transudate in nature and without infection (table 2). The lead placement was checked using cine fluoroscopy in AP and lateral position. (figure2:G,H) The patient was closely monitored in the intensive cardiac care unit for 3 days to check for any fluid re-accumulation. After that, the patient was transferred to the general ward and subsequently discharged. (figure 2: E, F).

Follow up

Following a one-month follow-up, the patient's symptoms improved. Echocardiography showed good left ventricle (LV) and right ventricle (RV) function with no pericardial effusion. The pacemaker (PPM) interrogation revealed consistent threshold levels as before, which we considered acceptable given the patient's age and frailty. The patient has been regularly followed up for the past two years and is doing well. (figure 3).

Discussion

Cardiac perforation due to pacemaker leads is a critical complication with a reported incidence of 0.4% to 2.0%.[2] This complication can occur at various intervals post-implantation, categorized as acute (within 24 hours), early (within 30 days), or late (beyond 30 days).[3] The majority of perforations present within a year of implantation, but late cases can occur up to several years post-procedure.[4] In this case, the patient presented 3 months after the PPM implantation. The management of lead perforation depends on the timing of presentation, symptoms, and the patient's overall health.

In this case, a thorough evaluation of the patient was conducted for other potential systemic causes of pericardial effusion considering tuberculosis, hypoalbuminemia, renal dysfunction, and malignancy. There were no signs/symptoms of pericarditis clinically and also on ECG. Tuberculosis was unlikely due to a non-contributory history. The laboratory results showed that pericardial fluid was transudate in nature with normal ADA levels and CB NAAT report. Additionally, the ESR was only mildly raised. The patient's Liver function was within normal limits with normal serum albumin levels. There were no signs or symptoms of malignancy, and the patient responded well to decongestive therapy. Pericardial fluid showed no abnormal cells on fluid cytology. Considering her age, the autoimmune cause is unlikely.

RV lead perforation can present with a range of symptoms from asymptomatic to severe manifestations

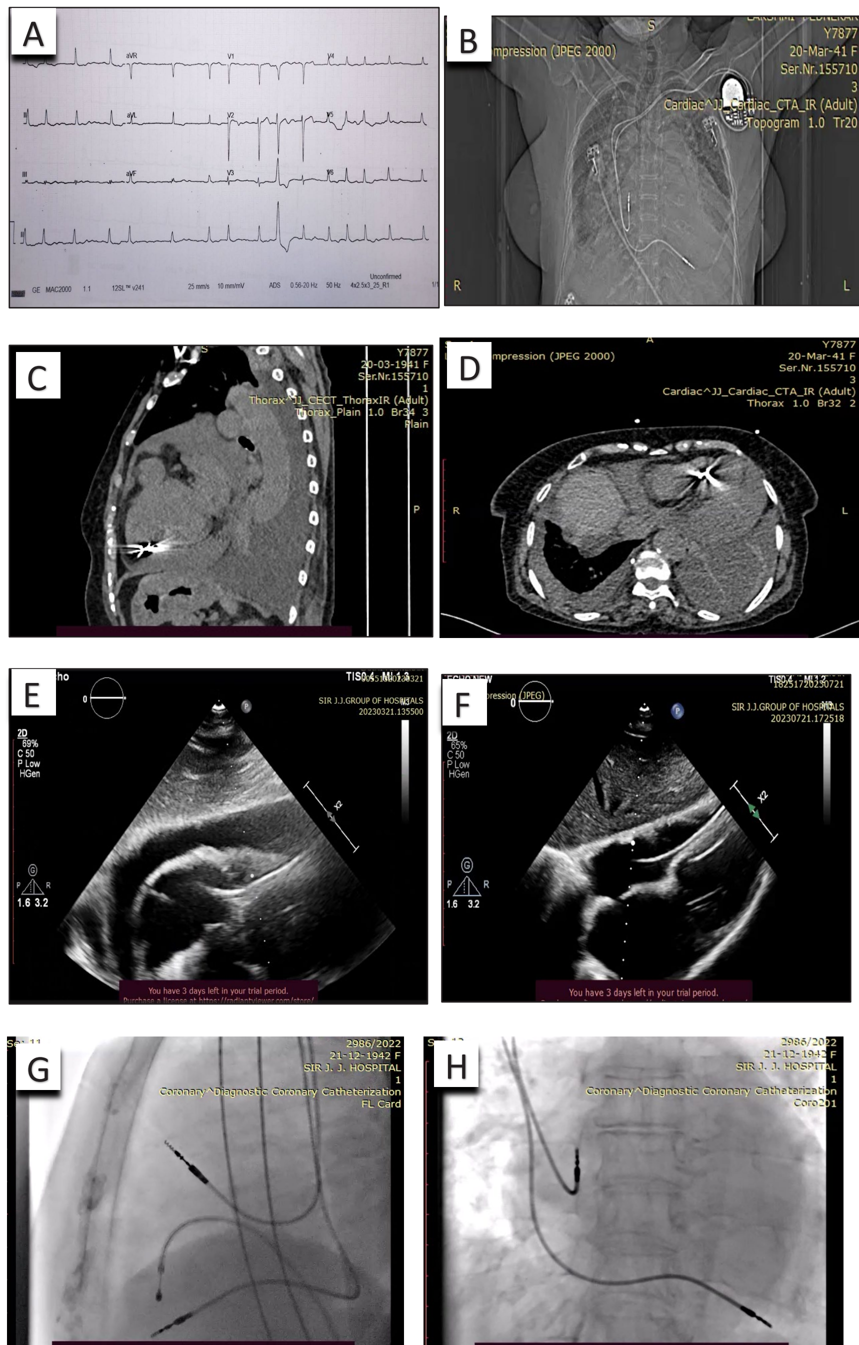

Figure 2. (A) ECG showing AF with fast ventricular rate with occasional VPC. (B) Chest X-ray shows pulmonary edema with cardiomegaly, bilateral blunted costophrenic angles, and a PPM pulse generator over the left side of the thorax with RA and RV leads in situ (Note: the RV lead position is beyond the heart border). (C) CECT Thorax sagittal cut section and. (D)Transverse cut section showing hyperdense RV lead tip within the pericardial space with moderate pericardial effusion. (E, F) 2D Echocardiogram subcostal view image before and after pericardiocentesis (Note: the RV lead position traversing across RV apex into pericardial space). (G, H) Lead placement was checked using cine fluoroscopy in AP and lateral position.

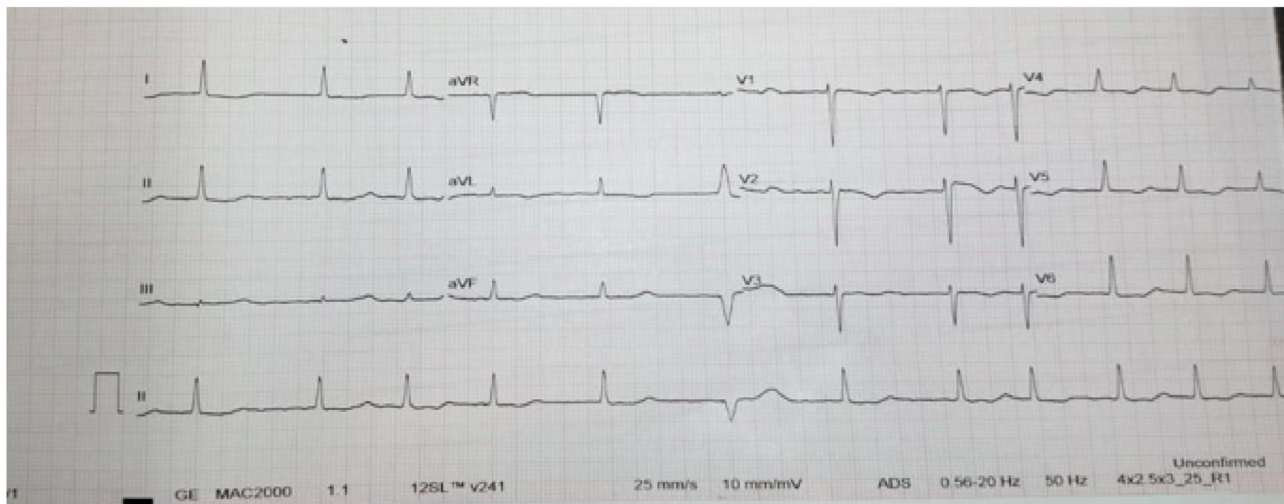

Figure 3. ECG on follow-up after a month.

like chest pain, dyspnoea, or signs of cardiac tamponade. Clinicians should maintain a high index of suspicion, especially in patients with persistent symptoms post-device implantation.[5,6] This patient had symptoms of biventricular failure.

Chest X-ray is often the first imaging modality to identify lead displacement or perforation. Echocardiography is useful for assessing pericardial effusion or signs of tamponade and evaluating lead position and complications. Computed Tomography (CT) offers detailed anatomical imaging to confirm perforation and visualize surrounding structures.[7] Fluoroscopy can be used during the diagnosis and management phases to guide lead repositioning or extraction.[8]

Immediate Management involves ensuring the patient is hemodynamically stable. If there is significant cardiac tamponade or severe symptoms, emergency pericardiocentesis may be required to relieve pressure.[9]

In many cases, percutaneous lead revision or extraction can be performed, especially when the perforation is identified early and the patient is stable.[10] The decision between revision and extraction depends on lead fixation, the extent of perforation, and associated complications. Extraction of the lead can be considered if the perforation is severe, associated with significant symptoms, or if there are signs of endocarditis or other complications. Recent studies highlight the safety and effectiveness of percutaneous lead extraction techniques.[11] The extraction may involve the use of mechanical sheaths and graspers, with fluoroscopic guidance.

For chronic or complicated cases, surgical intervention might be necessary.[12] In cases where extraction is not required or feasible, repositioning the lead to a different anatomical location within the RV or even into the coronary sinus may be considered. This approach requires careful guidance and imaging to avoid further complications.[13]

Patients who have experienced RV lead perforation should be monitored closely with regular follow-up visits, including echocardiograms or other imaging as needed, to ensure the lead remains in the proper position and to monitor for potential late complications.[14] Advanced cardiac devices often include remote monitoring systems to detect changes in lead performance or complications early.[15]

Independent predictors of cardiac perforation include: Patients over 80 years of age, female sex, body mass index (BMI) less than 20, patients who are on oral steroids in the week before implantation, placement of a ventricular lead in an apical position, use of a temporary pacemaker in conjunction with a permanent pacemaker, using a helical screw active fixation lead in the right ventricle and longer fluoroscopy times increases the risk of perforation.[16]

Factors that may reduce the risk of perforation include: Pulmonary hypertension, Right ventricular systolic pressure greater than 35 mmHg, and BMI greater than 30.[16]

Careful patient selection and preoperative assessment can help identify individuals at higher risk for lead-related complications, guiding more tailored approaches during device implantation[17] and ensuring optimal implantation techniques can reduce the risk of perforation.[18]

Summary

The management of RV lead perforation requires a multidisciplinary approach, balancing immediate intervention with long-term follow-up. The latest guidelines emphasize the importance of early detection, the use of advanced imaging techniques, and the availability of percutaneous and surgical options for lead management. Continuous advancements in technology and techniques are likely to further improve outcomes and safety for patients with this complication

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Conflict of Interest Statement

The authors declare no conflict of interest.

Consent to Participate

A well-informed written consent was obtained from the patient and relatives before the procedure.

Ethical Approval

Not applicable.

We declare that the paper is not under consideration elsewhere and none of the paper's contents have been published previously.

List of Abbreviations

AF Atrial Fibrillation
BMI Body Mass Index
CT Computed Tomography
CECT Contrast Enhanced Computed Tomography
DDDR Dual-chamber rate-modulated pacing
ECG Electrocardiogram
LV Left Ventricle
PPM Permanent Pacemaker
RV Right Ventricle
RA Right Atrium
VPC Ventricular Premature Complex

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