

Profile of sleep disordered breathing in heart failure with preserved ejection fraction

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Abstract

Heart failure (HF) with preserved ejection fraction (HFpEF) represents nearly half of HF cases and is increasingly being recognized as a cause of morbidity and mortality. Hypertension (essential or secondary) is an important risk factor of HFpEF, owing to permanent structural changes in heart. A common cause of secondary hypertension is obstructive sleep apnea (OSA). In the present study, we have attempted to seek the frequency and characteristics of sleep disordered breathing (SDB) in HFpEF. Also, we tried to investigate if any correlation exists between the severity

of SDB and the severity of diastolic dysfunction. This was a prospective, cross-sectional, case-control study in which 25 case patients with HFpEF and 25 control subjects were included. All the case patients and control subjects went through a detailed clinical, biochemical, echocardiography evaluation and overnight polysomnography. SDB was seen in 64% of the case patients having HFpEF and in 12% of control group with [odds ratio (OR)=12.2, 95% confidence interval (CI)=2.83-52.74; $p<0.001$]. A significant correlation of apnea hypopnea index (AHI) severity was observed with degree of diastolic dysfunction ($r=0.67$; $p<0.001$). Among HFpEF patients with SDB (16/25), 13 had OSA and only 3 had central sleep apnea (CSA). CSA was present in patients with severe diastolic dysfunction. There were no clinical or sleep quality differences among the OSA and the CSA group. To conclude, higher frequency of SDB is observed in HFpEF patients. AHI severity correlates with degree of diastolic dysfunction. The underlying mechanisms of correlation between SDB and diastolic dysfunction either through uncontrolled hypertension or direct causation warrant further evaluation.

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Key words: Heart failure; OSA; hypertension; diastolic dysfunction.

Conflict of interest: The Authors declare no conflict of interest relating to the study.

Informed consent: Written informed consent was taken.

Ethics approval: Institute ethical committee clearance was taken.

Contributions: All the Authors contributed to substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Received for publication: 21 April 2020.

Revision received: 7 September 2020.

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Licensee PAGEPress, Italy

Monaldi Archives for Chest Disease 2020; 90:1329

doi: 10.4081/monaldi.2020.1329

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Introduction

Heart failure (HF) is a common cause of cardiovascular morbidity and mortality and is a global health problem, affecting individuals in both developing and developed countries [1]. Despite improvements in therapy, the mortality rate in patients with HF has remained unacceptably high, making early detection of susceptible persons who would benefit from preventive measures imperative [2].

Epidemiological data have shown that the prevalence of sleep disordered breathing (SDB) is approximately 10% in the general population. In the heart failure with reduced ejection fraction population (HFrEF), SDB has been identified in up to 75% of cases, while in heart failure with preserved ejection fraction (HFpEF), existing data support a prevalence of SDB of approximately 55%.¹ The Sleep Heart Health Study, a prospective study comprising 6,424 men and women, indicated that the presence of Obstructive sleep apnea (OSA) (defined as an apnea hypopnea index, AHI ≥ 10 per h) favored the appearance of heart failure independently of other known risk factors, with a 2.20 relative risk [3]. The data suggest SDB may be a modifiable risk factor in HFpEF.

It is also hypothesized that the SDB may be associated with the onset and severity of hypertension, degree and severity of diastolic dysfunction, and that SDB may be an amenable factor in the management of HFpEF (Figure 1). A prospective cohort study of 1889 participants, during 21003 person-years of follow-up, in

comparison with participants without OSA concluded that the presence of OSA was associated with increased adjusted risk of incident hypertension [4]. Fung *et al.* investigated 68 OSA patients for parameters of diastolic dysfunction and stated that more severe SDB was associated with a higher degree of diastolic dysfunction [5]. Sidana *et al.* reported diastolic dysfunction was more prevalent in moderate-to-severe OSA [6].

Central sleep apnea (CSA) has been recognized more as a consequence than a cause of HF. The bidirectional relationship has potential therapeutic implications, given the evidence that the treatment of CSA can diminish sympathetic activity. However, the evidence of benefit of treating CSA is not as robust as for OSA. Optimizing treatment of heart failure in CSA is, therefore, more important before attempting positive airway pressure (PAP) therapy.

In the present study, we have attempted to seek the frequency and characteristics of SDB in HFpEF. Also, we tried to investigate, if any correlation exists between the severity of SDB and the severity of diastolic dysfunction.

Methods

The observational case-control study was carried out over a period of 18 months in the Department of Pulmonary, Critical care and Sleep Medicine, at the tertiary care center in North India. A total of 25 subjects in the age group of ≥ 50 years, diagnosed with HFpEF were recruited [1]. Exclusion criteria included acute congestive heart failure, acute coronary syndrome, stroke or renal failure. Age and sex matched family members without any cardiac illness and any clinical or echocardiographic evidence of heart failure were recruited as a control group. For the calculation of sample size, we considered the risk of SDB in HFpEF as 55% and in controls as 10%. We thus estimated a sample size of 25 per group at 80% power. Written informed consent was obtained from all the subjects. Institutional Ethical Committee (IEC) clearance was obtained. Data were collected from all the subjects on demographic, clinical (age, sex, sleep history including snoring, choking, sleep disturbances and Epworth Sleepiness Scale self-report), anthropometric (body mass index BMI in kg/m^2) and risk factors including arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease.

Hypertension (HTN) was determined when patients had systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg for more than two days in the stable phase, and those who were previously diagnosed with hypertension and were receiving hypertensive treatment. The degree of HTN was classified as stage 0 SBP < 140 mmHg and/or DBP < 90 mmHg; Stage 1 SBP 140 - 159 mmHg and/or DBP 90 - 99 mmHg; Stage 2 SBP 160 - 179 mmHg and/or DBP 100 - 109 mmHg; Stage 3 SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg as per European Society of Cardiology 2018 guidelines [7].

Transthoracic echocardiography (TTE) was done using Epiq 7 (Philips Respiroics, USA). Left ventricular ejection fraction (LVEF) measurement was done using modified biplane Simpson's rule [8]. LV end diastolic volume (LVEDV) and LV end systolic volume (LVESV) were obtained from apical four- and two-chamber views and DecT (deceleration time of MV-E); e' (early diastolic tissue velocity); E/e' (a ratio between early mitral inflow velocity and mitral annular early diastolic velocity); IVRT (isovolumetric relaxation time); MV-A (mitral valve late diastolic inflow) and MV-E (mitral valve early diastolic inflow) were measured. HFpEF was diagnosed when all the following three conditions were fulfilled [1]:

1. The presence of symptoms and/or signs of HF

2. A 'preserved' EF (defined as LVEF $\geq 50\%$ or 40 - 49% for HFmrEF)
3. Elevated levels of NPs (BNP > 35 pg/mL and/or NT-pro BNP > 125 pg/ml) along with relevant structural heart disease (Left atrial enlargement or left ventricular hypertrophy) or evidence of diastolic dysfunction.

Diastolic dysfunction was documented by a left atrial volume index (LAVI) > 34 ml/m^2 or a left ventricular mass index (LVMI) ≥ 115 g/m^2 for males and ≥ 95 g/m^2 for females or an $E/e' \geq 13$ and a mean e' septal and lateral wall < 9 cm/s. The degree of diastolic dysfunction was classified as per guidelines [1]. The patients underwent overnight, in-laboratory, supervised Polysomnography (PSG) (Alice 6 LDX (Philips Respiroics). The scoring was based on the criteria laid down in the International Classification of Sleep Disorders, third edition (ICSD-3). SDB was diagnosed at AHI > 5 /hour with symptoms of OSA (complains of sleepiness, non-restorative sleep, fatigue) or comorbidities (hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation or type 2 diabetes mellitus) [9].

All of the data obtained thereby were recorded systematically using Microsoft office excel and statistical analysis carried out using Statistical Package for Social Sciences version 21. The data were expressed as a mean, standard deviation, frequency and percentage and analyzed using parametric (*t*-test) and non-parametric (Mann-Whitney) tests. The correlation was determined using Spearman's coefficient of correlation. Statistical significance was set at 5% (corresponding to a p-value ≤ 0.05).

Results

The study cohort consisted of 25 diagnosed patients of HFpEF and 25 age and sex matched controls (healthy subjects). Hypertension (88%) was a common co-morbidity in HFpEF group. Significant ESS score was not present in either HFpEF patients or controls. However, history of Snoring was present in 64% of cases. Arterial blood gas analysis revealed a lower oxygen (po_2) in the HFpEF group along with high lactate (mean of 0.94 ± 0.13 as compared to 0.50 ± 0.06 , $p < 0.001$) levels as compared to controls (Table 1). HFpEF patients in comparison to controls had significantly lower sleep efficiency, longer WASO, longer N1 and N2 with shorter N3 and REM sleep stage (Table 1).

SDB was seen in 64% of the case patients and in 12% of control group with [odds ratio (OR) = 12.2, 95% confidence interval (CI) = 2.83-52.74; $p < 0.001$]. Patients with HFpEF and SDB in present study had a higher E/A ratio and a shortened IVRT compared to those without SDB, indicating that SDB may be associated with more severe diastolic dysfunction in HFpEF patients (Table 2). A significant correlation of AHI severity was observed with degree of diastolic dysfunction ($r = 0.67$; $p < 0.001$). Among HFpEF patients with SDB (16/25), 13 had OSA and 3 had CSA (Table 3). CSA was present in severe diastolic dysfunction patients. However, the sleep quality and arterial blood gas analysis was similar in both OSA and CSA groups (Table 4).

Discussion

Epidemiologic data have shown that the prevalence of SDB is approximately 10% in the general population [1]. SDB in HFpEF has been reported in variable frequency among various studies.

Bitter *et al.* from Germany, evaluated 244 patients with HFpEF; SDB was documented in 169 patients (69.3%), of these 97 patients (39.8%) presented with OSA [10]. A study by Chan *et al.*, from Hong Kong, showed that 55% of the patients (11/20) had significant SDB; 7 of these patients had predominantly obstructive sleep apnea (OSA) [11]. Herrscher *et al.*, from Norway, have also reported HFpEF patients had SDB in 80% of the cases, 62% had OSA [12]. The recent study by Akiwara *et al.* from Japan, reported presence of SDB in 67% of 58 patients under evaluation [13]. The criteria used for SDB, the method used for evaluating it and the degree of diastolic dysfunction contributes to these varied figures. In our study, from India, among 25 HFpEF patients, 16 had SDB (64%), of which 13 had OSA as the major SDB. The proportion of SDB in control group was only 12%; all of them diagnosed as OSA. This was documented by a level 1 PSG in all the patients included in the study.

We tried to seek a correlation between the severity of degree of diastolic dysfunction and SDB. We observed that, with increasing severity of diastolic dysfunction, there was an associated increase in AHI severity, decline in sleep efficiency, along with occurrence

of CSA in severe diastolic dysfunction patients. Various studies have indicated that with worsening diastolic dysfunction, SDB worsens. Bitter *et al.* [10] reported that with increasing impairment of diastolic function, proportion SDB and particularly CSA increased. Fung *et al.* [5] evaluated 68 OSA patients, reported that more severe SDB was associated with a higher degree of diastolic dysfunction. HF and CSA patients are characterized by a high sympathetic activation during both day and night. This sympathetic activation is linked to the frequency of apneas. Additionally, the frequency and severity of hypoxia through chemoreflex activation contribute to the degree of sympathetic activation. These mechanisms suggest that CSA can have a causative role in worsening the clinical condition of patients with HF, emphasizing the existence of a bidirectional relationship between two conditions.

In past studies, LV wall thickness has been shown to be increased in normotensive patients with OSA vs normotensive control subjects, suggesting that OSA by itself can cause LV hypertrophy and diastolic dysfunction apart from any effect on diurnal systemic BP [14,15]. Thus, OSA may have been an etiology of HFpEF in our patients, or may have worsened it by causing hypertension.

Table 1. Baseline characteristics and polysomnographic parameters of cases and controls.

Parameters	Cases (n=25) n (%)	Controls (n=25) n (%)	p
Gender			
Male	21 (84)	19 (76)	
Female	4 (16)	6 (24)	0.47
Age (mean±SD) (years)	60.5±9.8	57.9±6.5	0.22
BMI (mean±SD) (kg/m ²)	28.35±1.62	28.30±1.24	0.32
Snoring	16 (64.0)	4 (16.0)	<0.001
Hypertension	25 (100)	4 (6.25)	<0.001
Duration of hypertension (mean±SD) (years)	7.2±2.1	0.2±0.1	<0.001
Blood pressure [systolic (mean±SD) / diastolic (mean±SD)]	148.4±23.18 / 89.5±12.8	124.1±10.2 / 79.6±5.9	0.016
pH (mean±SD)	7.42±0.02	7.40±0.02	0.001
pCO ₂ (mean±SD) (mmHg)	37.17±1.51	40.26±1.30	<0.05
pO ₂ (mean±SD) (mmHg)	66.45±2.70	79.28±6.96	<0.001
HCO ₃ ⁻ (mean±SD) (meq/l)	22.20±1.14	24.04±0.80	<0.05
Lactate (mean±SD) (mmol/l)	0.94±0.13	0.50±0.06	<0.001
NT-ProBNP (mean±SD) (pg/ml)	500.28±201.73	62.56±18.31	<0.001
PSG (n)			
AHI <5	09 (36.0%)	22 (88.0%)	
AHI ≥5	16 (64.0%)	03 (12.0%)	<0.001
SDB (AHI ≥5 + signs/symptoms or medical disorder)	16 (88%)	3 (12%)	<0.001
PSG_TST	415.64±9.22	417.88±14.53	0.518
PSG_sleep_efficiency (%)	87.88±3.38	62.00±9.95	<0.001
PSG_sleep_onset (min)	8.94±1.63	14.60±3.04	<0.001
PSG_WASO (min)	64.80±4.25	120.10±11.98	<0.001
PSG_N1 (%TST)	22.76±1.31	28.01±8.18	0.003
PSG_N2 (%TST)	42.17±1.67	54.22±13.05	<0.001
PSG_N3 (%TST)	22.97±1.22	10.38±8.25	<0.001
PSG_R (%TST)	12.16±2.30	7.45±3.84	<0.001
AHI (mean ± SD)	7.64±4.49	2.56±2.22	<0.001
RDI (index) (mean ± SD)	8.08±4.40	2.56±2.22	<0.001
Snoring episodes (mean ± SD)	56.36±36.44	31.56±25.00	0.007
Average HR (mean ± SD)	84.40±8.12	69.97±7.28	<0.001

BMI, body mass index; HCO₃⁻, bicarbonate level; NT, ProBNP-N-terminal pro b-type natriuretic peptide; HCO₃⁻, bicarbonate level; PSG, polysomnography; TST, total sleep time; WASO, wake time after sleep onset; AHI, apnea hypopnea index; RDI, respiratory disturbance index. All p-values calculated using Fischer Exact Test.

In the present study, on evaluation of sleep quality by PSG, HFpEF patients in comparison to controls had similar TST, but had significantly lower sleep efficiency, longer WASO, longer N1 and N2 with shorter N3 and REM sleep stage. This difference in WASO, N1, N2 and N3 were not seen among the HFpEF with SDB and without SDB groups. The finding is consistent with previous studies [16-18]. ACC/AHA guidelines have identified lack of or poor sleep as a barrier to self-care and treatment adherence in HF patients, providing yet another route to increased risk of morbidity and mortality [1]. The absence of deep sleep, excess stage 1 sleep, and frequent arousals, along with insomnia and wakefulness, collectively could result in increased heart rate and sympathetic activity, with deleterious cardiovascular effect. This state of autonomic imbalance increases blood pressure and heart rate, contributing to the progressive nature of chronic heart failure [19,20].

HFpEF patients with SDB may be candidates for treatment of the underlying SDB with aim to prevent recurrence and improve quality of life. A few recent studies have shown evidence that positive airway pressure (PAP) treatment in patients with HFpEF and OSA has improved respiratory function (AHI), functional capacity (cardiopulmonary exercise testing), cardiac function and NYHA functional class [10,18]. In an observational prospective study by Yoshisha *et al.*, treated 109 HFpEF patients with adaptive servo ventilation (ASV) (n=31) vs usual care (n=78), followed up of 6 months and found a decrease in cardiac death and hospitalizations due to cardiac disease (p<0.05), demonstrating

mortality benefit of ASV in HFpEF patients [21]. However, ASV was associated with increased all-cause and cardiovascular mortality in patients who had HFrEF with predominantly central sleep apnea. The ADVENT-HF study is enrolling patients with ejection fraction below or equal to 45% with OSA (without excessive daytime sleepiness) or CSA [22].

Thus, identifying the predominant SDB, whether OSA or CSA is important as PAP therapy will be the treatment of choice for OSA and will also help in improving cardiac function and functional capacity. Whereas, treating CSA with PAP may or may not be as beneficial for the patient. Differentiating them is best possible by a level 1 PSG with thoracic and abdominal belts to evaluate the effort with the apnea/hypopnea. Most of the reported literature is of home sleep study or a level 3 PSG. Besides, in our study, sleep quality and laboratory parameters in OSA and CSA patients were found comparable as shown in Table 4, thereby providing no potential of predicting the dominant SDB without a PSG.

Limitations and strengths

A limitation of our study was the small sample size; we had only 25 patients, and we had insufficient numbers for subgroup analysis. We excluded acute heart failure patients; hence our cohort may not be representative of the whole heart failure population seen

Table 2. Polysomnography, arterial blood gas and echocardiography of HFpEF patients with and without sleep disordered breathing.

Variable	SDB present(n=16)		SDB absent(n=9)		p
	Mean	SD	Mean	SD	
Age (years)	58.7	9.5	63.7	10.0	0.228
BMI (kg/m ²)	28.2	1.6	28.6	1.8	0.587
Duration (years)	3.0	1.3	3.1	1.4	0.884
pH	7.4	0.0	7.4	0.0	0.899
PCO ₂ (mmHg)	40.3	1.5	40.0	1.6	0.609
PO ₂ (mmHg)	66.2	2.9	66.8	2.4	0.624
HCO ₃ (meq/l)	24.3	1.3	24.0	0.8	0.521
Lactate (mmol/l)	1.0	0.1	0.9	0.1	0.102
NT-ProBNP (pg/ml)	523.8	230.3	458.4	139.8	0.448
PSG_TST (min)	419.6	15.6	414.8	12.6	0.435
PSG_sleep_efficiency (%)	58.6	7.7	68.0	11.1	0.02
PSG_sleep_onset (min)	14.1	3.1	15.4	2.9	0.323
PSG_WASO (min)	121.5	11.1	117.6	13.7	0.446
PSG_N1 (%TST)	27.7	8.7	28.6	7.6	0.802
PSG_N2 (%TST)	57.9	13.3	47.6	10.2	0.055
PSG_N3 (%TST)	8.1	8.1	14.4	7.2	0.067
PSG_R (%TST)	6.2	3.2	9.6	4.2	0.033
PSG_A+H (index)	9.9	4.2	3.7	1.1	<0.001
PSG_snoring episodes	59.8	41.9	40.6	14.6	0.198
PSG_avg HR (/min)	87.7	6.0	78.6	8.4	0.004
Echo_ejection fraction (%)	55.84	2.01	52.08	3.24	<0.001
Echo_deceleration time (m/s)	191.52	51.23	185.52	45.74	0.664
Echo_early filling/atrial filling (E/A) (m/s)	1.06	0.17	1.50	0.65	0.002
Echo_isovolumic relaxation time (m/s)	135.72	19.41	84.68	27.59	<0.001

SDB, sleep disordered breathing; BMI, body mass index, HCO₃, bicarbonate level; NT-ProBNP, N-terminal pro b-type natriuretic peptide; PSG, polysomnography; TST, total sleep time; WASO, wake time after sleep onset; A+H- apnea+hypopnea; HR, heart rate.

Table 3. Obstructive sleep apnea and central sleep apnea patients in HFpEF.

Variable		OSA (n=13)		CSA (n=3)	
		Count	%	Count	%
Sex	Male	11	84.6	2	66.7
	Female	2	15.4	1	33.3
Dyspnea (NYHA)	2	4	30.8	0	0.0
	3	6	46.2	2	66.7
	4	3	23.1	1	33.3
Epworth sleepiness score	0	9	69.2	0	0.0
	1	1	7.7	1	33.3
	2	0	0.0	2	66.7
	3	1	7.7	0	0.0
	4	1	7.7	0	0.0
	6	1	7.7	0	0.0
SDB_snoring		10	76.9	3	100
Choking		4	30.8	2	66.7
Sleep disturbance		6	46.2	3	100
Hypertension		12	92.3	3	100
Stage of hypertension	0	1	7.7	0	0.0
	1	7	53.8	0	0.0
	2	5	38.5	2	66.7
	3	0	0.0	1	33.3
No of drugs for hypertension	0	1	7.7	0	0.0
	1	10	76.9	0	0.0
	2	2	15.4	2	66.7
	3	0	0.0	1	33.3
Grade of diastolic dysfunction	1	5	38.5	0	0.0
	2	5	38.5	0	0.0
	3	3	23.1	3	100

OSA, obstructive sleep apnea; CSA, central sleep apnea; NYHA, New York Heart Association; SDB, sleep disordered breathing.

Table 4. Arterial blood gas analysis and polysomnography findings of OSA and CSA patients in HFpEF.

Variable	OSA (n=13)		CSA (n=3)		p
	Mean	SD	Mean	SD	
Age	58.4	9.8	60.0	10.0	0.801
BMI	27.9	1.6	29.4	0.6	0.142
Duration (years)	2.9	1.1	3.5	2.2	0.493
ABG_pH	7.4	0.0	7.4	0.0	0.835
ABG_PCO ₂	40.3	1.6	40.0	1.7	0.760
ABG_PO ₂	66.5	2.6	64.9	4.6	0.408
ABG_HCO ₃	24.3	1.3	24.3	1.3	0.948
Lactate	1.0	0.1	1.0	0.1	0.906
NT-ProBNP	471.3	218.8	751.3	122.1	0.054
PSG_TST	417.5	14.2	428.7	21.5	0.281
PSG_sleep_efficiency (%)	60.2	7.2	51.7	6.7	0.082
PSG_sleep_onset (min)	14.4	3.4	13.2	1.4	0.589
PSG_WASO (min)	121.1	12.3	123.1	2.6	0.796
PSG_N1 (%TST)	28.2	7.0	25.3	16.2	0.620
PSG_N2 (%TST)	57.9	12.9	58.2	17.8	0.968
PSG_N3 (%TST)	7.9	8.9	9.1	4.1	0.832
PSG_R (%TST)	6.0	3.4	7.4	2.2	0.515
PSG_A+H (index)	9.1	4.0	13.2	3.3	0.121
PSG_snoring episodes	61.8	45.5	51.0	23.9	0.700
PSG_avg HR	87.4	5.3	89.0	10.0	0.691

BMI, body mass index; ABG, arterial blood gas analysis; HCO₃, bicarbonate level; NT-ProBNP, N-terminal pro b-type natriuretic peptide; PSG, polysomnography; TST, total sleep time; WASO, wake time after sleep onset; R, random eye movement; A+H- apnea+hypopnea; HR, heart rate.

frequently in routine clinical practice. The strength of present study was evaluation was done using level 1 PSG. This allowed for characterization into central and obstructive apneas and labelling the profile on the basis of the dominant disorder. Furthermore, blinded visual analysis of all polysomnographic data was performed at a single center thus minimizing inter-observer variability.

Conclusions

In conclusion, given the high frequency of SDB, especially OSA, in HFpEF patients, the effects on degree of impairment of diastolic function, and the possibility of improvements with PAP therapy, screening for SDB in all HFpEF patients may be justified, notably in those who have snoring and hypertension. The patients with OSA should be offered PAP therapy in a pursuit of improved outcomes. The SDB must be evaluated by a level 1 PSG as these patients may have co-existing CSA, treatment of which needs to be individualized besides optimizing heart failure medications.

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