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ORIGINAL RESEARCH ARTICLE

Sympathetic activation in heart failure with reduced and mildly reduced ejection fraction: the role of aetiology

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Abstract

Aim While sympathetic overactivity in heart failure (HF) with reduced ejection fraction (HFrEF; EF $<$ 40%) is well-documented, it is ill-defined in patients with mildly reduced EF (HFmrEF; EF 40–49%). Furthermore, the significance of ischaemic versus non-ischaemic aetiology in sympathetic activation is also unclear and has yet to be studied in HF. Our goal was to compare muscle sympathetic nerve activity (MSNA) in HFmrEF and HFrEF patients and in healthy subjects, as well as to elucidate the influence of the underlying disease.

Methods and results Twenty-three HFrEF (age 58 ± 10 years), 33 HFmrEF patients (age 61 ± 10 years), including 11 subjects with non-ischaemic cardiomyopathy in each HF groups and 10 healthy controls (age 55 ± 10 years), were studied. MSNA—detected by peroneal microneurography, continuous arterial pressure, and ECG—was recorded. MSNA frequency (burst/min) and incidence (burst/100 cycles) were calculated. Association with the patients' characteristics were assessed, and aetiology-based comparisons were performed. Burst frequency demonstrated a significant stepwise increase in both HFmrEF (41 ± 11 burst/min) and HFrEF (58 ± 17 burst/min, $P < 0.001$) patients as compared with controls (27 ± 9; $P < 0.001$ for both HF groups). Similarly, burst incidences were 66 ± 17, 82 ± 15, and 36 ± 10 burst/100 cycles in HFmrEF, HFrEF patients, and in healthy controls, respectively ($P < 0.001$ for all). Burst frequencies in HF patients showed significant correlation with NT-proBNP levels, and significant inverse correlations with the subjects' mean RR intervals, stroke volumes, pulse pressures, and EF.

Conclusions Muscle sympathetic nerve activity parameters indicated significant sympathetic activation in both HFmrEF and HFrEF patients as compared with healthy controls with no difference in relation to ischaemic versus non-ischaemic aetiology.

Keywords Baroreflex; Heart failure; Ejection fraction; Muscle sympathetic nerve activity

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Introduction

Left ventricular ejection fraction (LVEF) is a significant parameter of heart failure (HF). For a long time, our attention had been focused on the HF population with reduced ejection fraction, (HFrEF), before another subgroup currently classified as heart failure with preserved ejection fraction (HFpEF) was recognized. This classification, however, left a gap for an intermediate group, which has remained largely neglected.[1] Recently, the European Society of Cardiology (ESC) in its updated heart failure guidelines introduced the new category of heart failure with mildly reduced ejection fraction (HFmrEF, LVEF 40–49%).[2] The same guidelines also confirmed the definitions of HFrEF and HFpEF, using LVEF categories of $<$40% and LVEF $\geq$ 50%, respectively. HFmrEF is a sizable subgroup, encompassing one fifth of heart failure patients.

The epidemiology, aetiology, characteristics, treatment, and long-term outcome of this new entity are currently topics of intense research.[3–5]

It has been long recognized that parasympathetic withdrawal is a typical feature of HF.[6] Sympathetic neural overdrive, as assessed by the direct method of multi-unit MSNA recording, is characterized by increased sympathetic discharge and progressive loss of rhythmic sympathetic oscillations.[7–10] Elevated MSNA in heart failure has also been recognized as a marker of poor prognosis.[11] Although in certain studies severe and moderate heart failure subgroups were compared,[12,13] most studies concentrated on the sickest HFrEF population. Limited observations on HFpEF subjects indicated that this subgroup could also feature sympathetic overactivity.[14–16] Even less data exist concerning sympathetic regulation in the HFmrEF population. Most recently, Seravale *et al*. reported MSNA studies in heart failure subgroups: HFrEF, HFmrEF, and HFpEF, compared with healthy volunteers.[17] They found a gradual and significant increment in MSNA activity from healthy controls to HFrEF.[17]

The role of the underlying aetiology of HF in sympathetic activation is still debated. Certain groups detected greater sympathetic activation in HFrEF patients with an ischaemic aetiology, compared with a non-ischaemic one.[18] Nevertheless, other researchers found no such differences.[19] HFrEF and HFmrEF subjects share common features, including the high prevalence of ischaemic aetiology.[20] The transitioning of HFmrEF patients to a better or worse ejection fraction category is quite frequently observed.[5] The trajectory of changes may be related to a difference in aetiology, which therefore deserves special attention.

Our goal was to compare MSNA in groups of HFrEF and HFmrEF patients and in healthy volunteers and to assess the role of HF aetiology within these subgroups. The relationship between the clinical and laboratory characteristics of heart failure and MSNA was also to be addressed.

Methods

Patients

Ambulatory heart failure (HF) patients on optimized medical therapy who had been stable for at least 3 months were recruited from the outpatient clinics of the Department of Cardiology at the University of Debrecen and considered for participation. Patients with valvular heart disease, atrial fibrillation, or diabetes mellitus were excluded. No patients with ventricular pacemaker rhythm or frequent extrasystole were included. Prior to their study, all patients were screened for the signs of neuropathy, and positive cases were also excluded. Our study complied with the Declaration of Helsinki and was also approved by the ethical committee of the University of Debrecen. Informed written consent was provided by all participants. Healthy controls were recruited from the faculty and health care workers of the hospital. All healthy volunteers were screened with echocardiography prior to entering the study, and none of them showed signs of cardiac disease.

Autonomic studies

Studies were performed in our dedicated autonomic laboratory. The subjects were instructed to refrain from caffeinated beverages on the day of the study. Surface electrocardiogram and beat-to-beat arterial pressure (Finapres model 2300, Ohmeda) were recorded. The breathing rate was followed by the noncalibrated pneumobelt signal. MSNA was recorded by inserting a tungsten microelectrode with uninsulated tip diameters of 1–5 μm (Frederick Haer, Bowdoinham, ME) into the right common peroneal nerve, with a subcutaneous reference electrode in close proximity. Both electrodes were connected to a differential preamplifier and then to an amplifier (total gain of ~70 000), where the nerve signal was band-pass filtered (700–2000 Hz) and integrated (time constant 0.1 s) to obtain a mean voltage display of nerve activity (Nerve Traffic Analyser, model 662C-4, Bioengineering, University of Iowa).

Signals were sampled at 500 Hz and digitized with processing software (WinDaq, Dataq Instruments, Akron). Data were imported into a customized software program for analysis (Absolute Aliens Ay, Turku, Finland, WinCPRS). R-waves on the ECG as well as systolic and diastolic arterial pressure values were detected automatically by the program and then edited by the investigators. The stroke volume was calculated from the Finapres signal by the WinCPRS software, based on arterial pulse contour analysis.[21] Bursts of multi-unit MSNA were identified within a 0.5 s window, centred on an expected burst peak latency from preceding R-waves of 1.3 s.[22] Muscle sympathetic nerve bursts were automatically detected on the basis of amplitude using a signal-to-noise ratio of 3:1. MSNA was expressed as burst frequency (in bursts/min) and burst incidence (in bursts/100 heart beats). Over a 5 min recording period, diastolic pressure values were grouped in 3 mmHg bins. Taking the aforementioned latency into consideration, the sympathetic burst incidence was plotted against the mean of the bins, and the slope of the correlation served as sympathetic baroreflex (BRSsy). Only correlations with $r > 0.5$ were accepted.

Additional examinations

Echocardiography

Although the participants were selected on the basis of their previous echocardiograms, a confirmatory echocardiography was repeated right before the MSNA studies, and these

results were entered into our database. The examinations were performed in all patients using the Epiq 7C (Philips Medical Systems, Andover, MA), equipped with the X5-1 transducer. The left ventricular ejection fraction was determined by the biplane method of disks (modified Simpson's rule).

The vital parameters were recorded, blood samples were taken for N-terminal proBNP (NT-proBNP) determination on the day of MSNA study, and a 6-min walk test was also performed. Expected age- and gender-adjusted 6-min walking distances (6MWD) were calculated by standard formulas.[23] The actual performance was categorized as 'normal' (equal or greater than expected) or 'abnormal' (less than expected). Those patients who were unable to perform the test because of their heart failure symptoms were automatically classified as abnormal 6MWD. Subjects who could not perform the test due to musculoskeletal disorders were excluded from the 6MWD analysis.

Statistics

Statistical analysis was carried out with the IBM SPSS (version 26; Chicago, Illinois USA) software. The normality of the data was evaluated with the Kolmogorov–Smirnov test. Mann–Whitney *U* or Kruskal–Wallis one-way nonparametric test was used to compare groups. Correlation analysis was performed with Spearman's rank correlation test. A *P* value <0.05 was considered statistically significant.

Results

Between June 2018 and February 2020, all consecutive patients who met the inclusion criteria and did not meet the pre-defined exclusion criteria were approached for recruitment in the study. In 56 cases (23 HFrEF and 33 HFmrEF), good quality multi-unit MSNA recordings were taken. The remaining 24 subjects were excluded from any further analysis, because no MSNA signal of sufficient quality could be obtained. Ten healthy volunteers also underwent successful MSNA recording (*Figure* 1). Characteristics of the subgroups are summarized in *Table 1*. The medications of the patients are shown in *Table 2*, the daily beta-blocker doses are expressed in carvedilol equivalent doses.[24] For all heart failure patients participating in the study, the heart rate and the sympathetic burst parameters were not statistically different among those treated with beta-blockers (n = 45) and without beta-blocker medications (n = 11).

Figure 1 Samples of representative MSNA recordings of two subjects from the HFrEF, HFmrEF, and healthy control groups each.

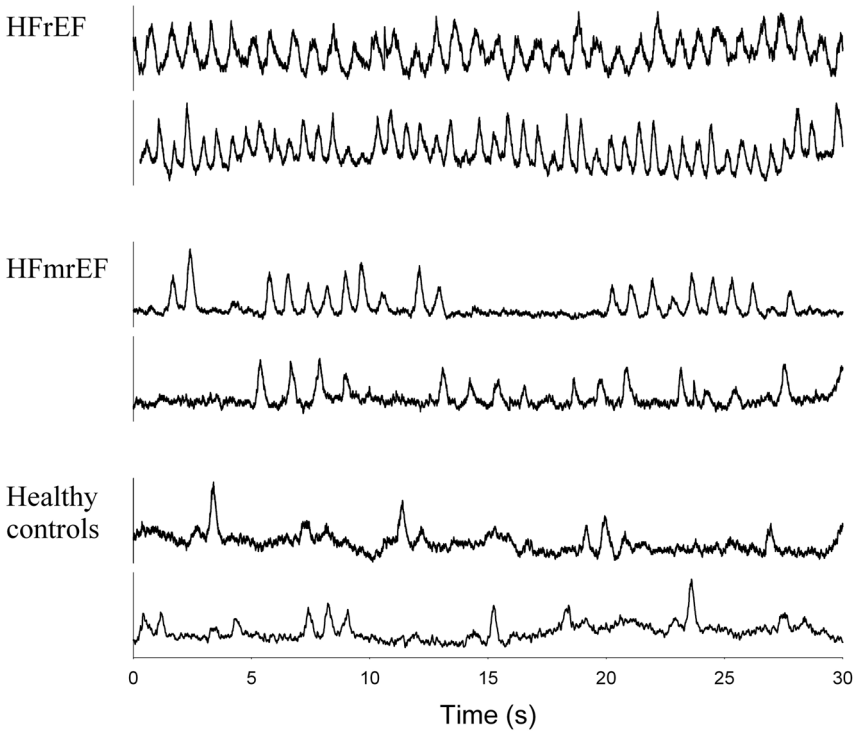

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Table 1 Demographic and clinical features of the studied subgroups

	Healthy volunteers (n = 10)	HFmrEF (n = 33)	HFrEF (n = 23)	*P*		
				Healthy vs. HFmrEF	Healthy vs. HFrEF	HFmrEF vs. HFrEF
Male	7	31	18	0.07	0.7	0.11
Female	3	2	5			
Ischaemic origin	-	22	12	-	-	NS
Non-ischaemic origin		11	11			
	-			-	-	NS
NYHA	-			-	-	0.002
NYHA I-II		32	14			
NYHA III-IV		1	9			
6MWD	-			-	-	NS
Normal		20	8			
Abnormal		6	11			
Age (year)	55 ± 10	61 ± 10	58 ± 10	0.08	0.52	0.12
BMI (kg/m^2)	25 ± 4	31 ± 4	29 ± 4	0.002	0.05	0.10
EF (%)	-	44 ± 4	27 ± 9	-	-	<0.001
NT-proBNP	16 ± 16	297 ± 229	2661 ± 3571	<0.001	<0.001	<0.001
Breathing rate	12 ± 3	19 ± 4	19 ± 5	<0.001	<0.001	0.60
Systolic pressure (mmHg)	151 ± 14	135 ± 21	1281 ± 20	0.07	0.012	0.49
Diastolic pressure (mmHg)	83 ± 10	70 ± 15	75 ± 11	0.02	0.26	0.36
Pulse pressure (mmHg)	68 ± 12	66 ± 13	53 ± 17	0.86	0.02	0.004
Heart rate (b.p.m.)	69 ± 7	63 ± 8	70 ± 12	0.13	0.94	0.01
RRI mean (ms)	877 ± 97	976 ± 124	892 ± 156	0.03	0.63	0.08
RRI Dev (ms)	35 ± 15	32 ± 17	25 ± 17	0.38	0.07	0.07
Cardiac index (L/min/m^2)	3.6 ± 1.0	3.2 ± 0.8	2.5 ± 1.2	0.28	0.01	0.02
Stroke volume index (mL/m^2)	51 ± 10	51 ± 15	38 ± 17	1	0.02	0.002

6MWD, 6 min walking distance; BMI, body mass index; BRSsy, sympathetic baroreflex sensitivity; NT-proBNP, N-terminal proBNP; RRI Dev, standard deviation of RR intervals; RRI mean, mean RR interval.

Table 2 Medications of the studied heart failure subgroups

	HFrEF	HFmrEF	*P*
Beta-blockers	21/23 (91%)	26/33 (79%)	NS
Beta-blocker Carvedilol equivalent Dose	26 ± 18 mg	26 ± 13 mg	NS
ACE/ARB	21/23 (91%)	29/33 (88%)	NS
MRA	22/23 (96%)	20/33 (60%)	0.004
Ivabradine	6/23 (26%)	3/33 (9%)	NS
Furosemide	20/23 (87%)	30/33 (91%)	NS

ACE/ARB, angiotensin convertase inhibitors/angiotensine receptor blockers; MRA, mineralcorticoid receptor antagonists.

Both HF patient populations had significantly larger BMIs than the controls. The breathing rate at rest in both HF patient groups was significantly higher than in controls (*Table 1*).

All but one patient in the HFmrEF group belonged to the NYHA I or II functional classes. In contrast, 64% of the participants in the HFrEF group belonged to the NYHA III or IV, and only 36% to the NYHA I–II functional classes (P = 0.002). The 6 min walk test was not performed by 11 patients, because of limitations imposed by their musculoskeletal disease, and 4 patients from the HFrEF group were exempted from the test because of severe heart failure symptoms (i.e. dyspnoea at rest). The 6MWD was abnormal in 29% of patients in the HFmrEF group and in 58% in the HFrEF group (P = NS)

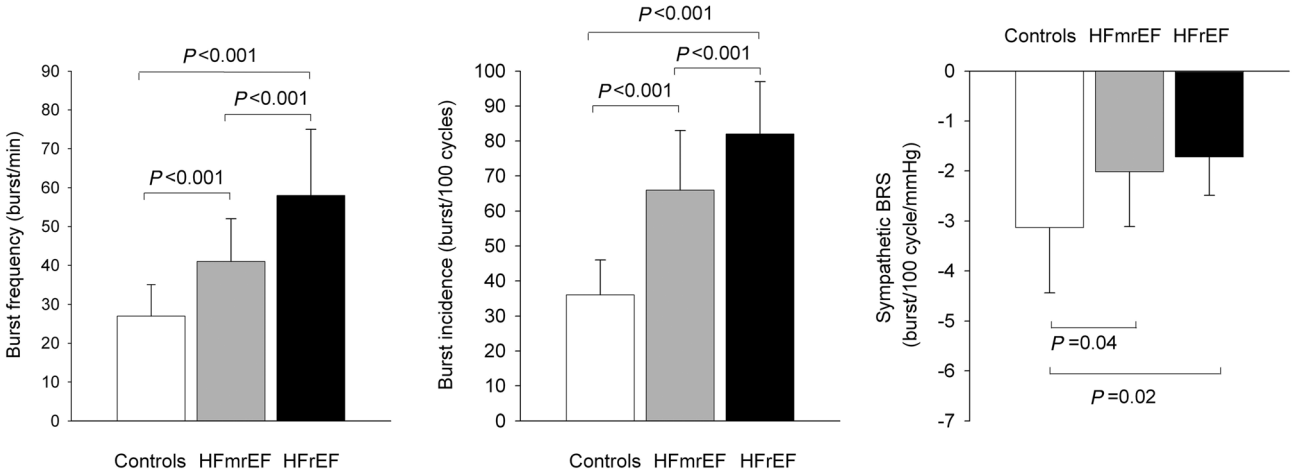
There was a large variation in the NT-proBNP levels of the HF groups. While the average levels in the HFmrEF group demonstrated only a mild elevation, an almost tenfold increase was detected in HFrEF patients ($P < 0.001$ for HFmrEF vs. HFrEF, and for both vs. controls) (*Table 1*).

The resting mean RR intervals in patients with HFmrEF were significantly longer than in the other two groups. The standard deviation of RR intervals (SDRR), on the other hand, was significantly decreased in the HFrEF group. Systolic and diastolic pressures were similar in the three cohorts. Pulse pressure was identical in the control and HFmrEF groups (66 ± 13 mmHg); however, it was significantly decreased in the HFrEF group (53 ± 17 mmHg). The stroke volume and cardiac output indices of the HFrEF group were significantly lower as compared with controls and to HFmrEF subjects (*Table 1*).

Sympathetic burst frequency (burst/min) and incidence (burst/100 cycles) showed significant elevation from control to HFmrEF groups, and a further significant elevation from HFmrEF to HFrEF (*Table 1*, *Figure 2*). BRSsy could be calculated in all control subjects; however, owing to low correlation, only in 48% in the HFrEF group and in 60% in the HFmrEF group was this index determinable. No difference was seen between BRSsy in the two heart failure groups, but both were significantly decreased compared with controls (*Table 1*, *Figure 2*).

Combining the HF subjects, (n = 56), the interrelationship between sympathetic activity and other clinical and laboratory parameters was assessed. The burst frequency showed significant inverse correlations with mean RR intervals, EF, stroke volume index, and pulse pressure (*Figure 3*). Because

Figure 2 MSNA burst frequency, burst incidence, and BRSsy in the HFrEF, HFmrEF, and the healthy control groups. Values represent mean ± SD.



NT-proBNP levels showed an extremely wide variation among the subjects, these values were correlated to burst frequency following logarithmic transformation (*Figure 3*). Burst incidence showed significant correlation only with NT-proBNP levels and EF (not shown).

All studied HF subjects who belonged to NYHA III–IV categories had a significantly higher burst frequency than those who belonged to categories I–II (58 ± 19 vs. 46 ± 15 burst/min; $P = 0.04$). A similar tendency was seen in the burst incidence (82 ± 15 vs. 70 ± 18 burst/100 cycles); however, the difference was not of significant extent. Subjects with abnormal 6MWD had significantly higher burst frequency than those with normal 6MWD (54 ± 17 vs. 42 ± 13 burst/min; $P = 0.01$). For burst incidence, (88 ± 18 vs. 78 ± 18) the difference was not significant.

Non-ischaemic was the origin of heart failure in 22 subjects (11 patients each in the HFrEF and in the HFmrEF groups). When combining the data of all HF patients, the only significant difference was found in the subjects' age; 55 ± 10 year in the non-ischaemic versus 63 ± 10 year in the ischaemic cohorts ($P = 0.009$). The burst activity and burst incidence of ischaemic patients (46 ± 16 burst/min and 71 ± 17 burst/100 cycles) were similar to the values of non-ischaemic subjects (52 ± 17 burst/min and 75 ± 19 burst/100 cycles, P = NS). Similar results were obtained when the HFrEF and HFmrEF groups were analysed separately (*Figure 4*).

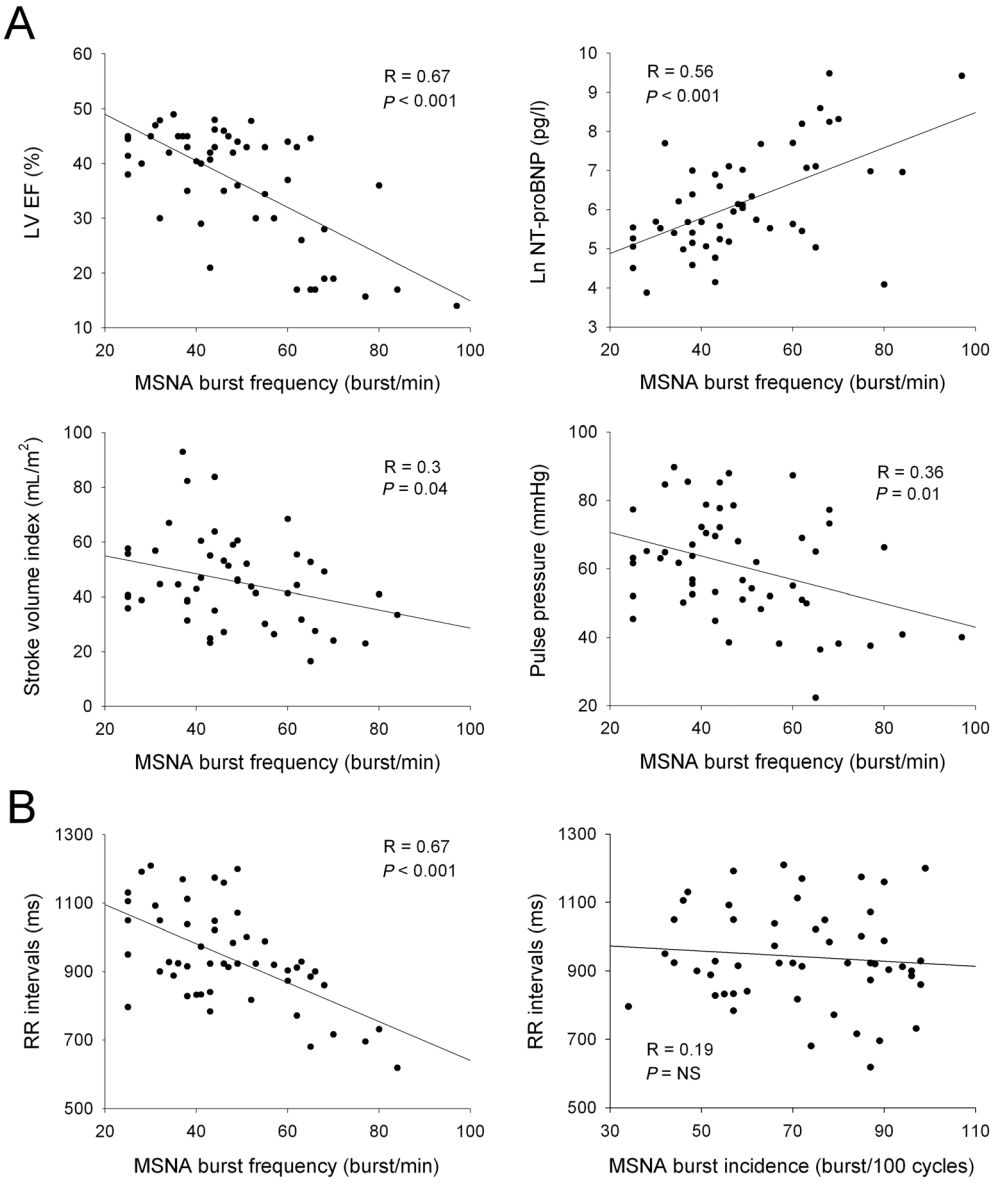
Discussion

The main finding of our study is that MSNA frequency and incidence in the HFmrEF group are not only significantly higher than in healthy controls but also significantly lower than in the HFrEF population. We have confirmed that in patients with HFrEF, the aetiology of heart failure does not influence sympathetic activation. Our study is the first to document that the same relationship applies to patients in the HFmrEF group.

Although the evidence of increased sympathetic activity in patients with severe heart failure is abundant, the activity in groups suffering from moderate heart failure is less documented. Recently, Seravale *et al*. reported observations on the MSNA of 9 HFrEF, 10 HFmrEF patients, and 14 healthy controls.[17] Their findings were similar to ours with regard to the significant stepwise increase in sympathetic activity from healthy to HFmrEF, then to HFmrEF to HFrEF subjects.[17] Our present study confirms their report in a larger patient population. Increased BMI, which could have been related to inactivity-induced weight gain or in certain cases to fluid accumulation in both heart failure subgroups, presumably contributed to their increased sympathetic activation.

Although the burst incidence-based BRSsy of both HF subgroups in our study were significantly decreased compared with controls, no significant difference was observed between the HFrEF and HFmrEF subgroups (*Figure 2*). BRSsy, however, unlike burst frequency or burst incidence, could not be determined in a substantial portion of the patients. Our previous analysis indicated that the lack of calculable BRSsy (due to low correlation) was associated in the heart failure populations with a very high burst incidence.[25] Therefore, the recordings of the subjects with the highest sympathetic activity, occurring mostly among HFrEF patients, were unsuited for this analysis. Spontaneous sympathetic gain could be calculated not only on the basis of burst incidence, but also by other methods which consider MSNA burst amplitude or burst area as well. This latter index, however, is also frequently incalculable even in healthy subjects.[26]

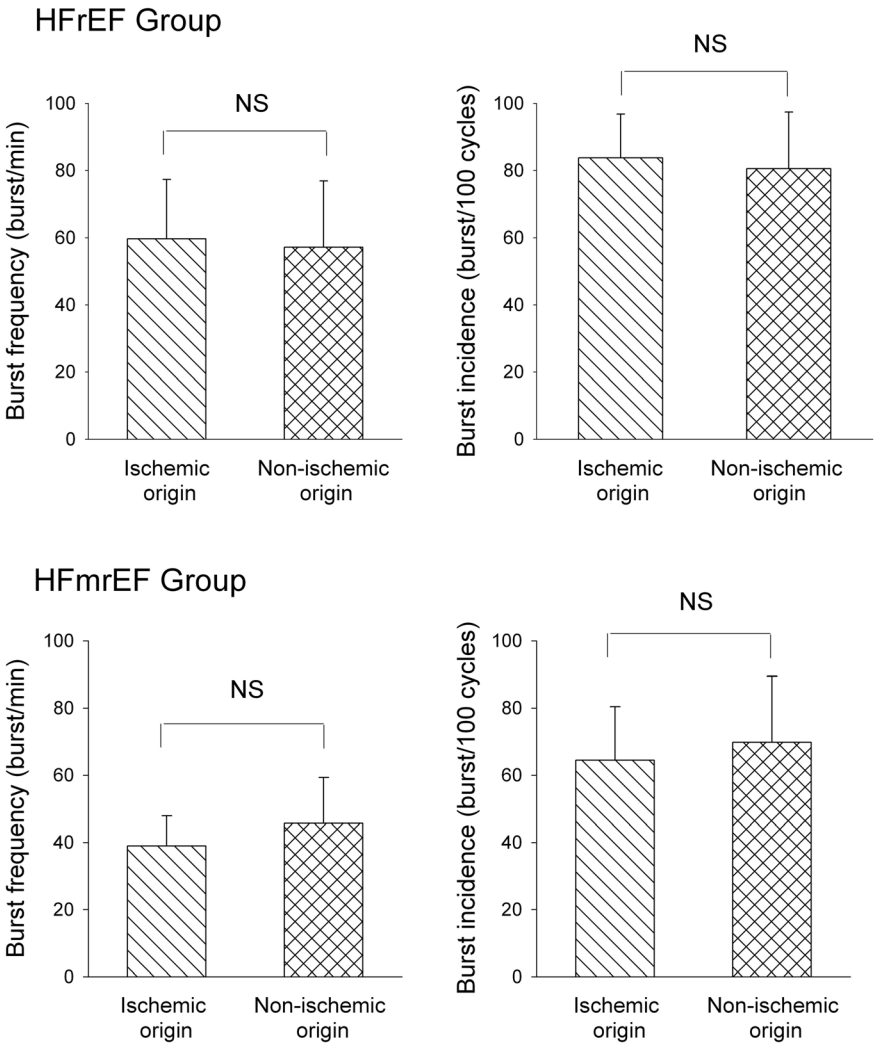
Figure 3 Figures in panel (A) show the correlations between the subjects' MSNA burst frequency and other characteristics, including EF, stroke volume index, pulse pressure, and the logarithmically transformed NT-proBNP parameters. The figure on the left in panel (B) shows the close inverse relationship between the subjects MSNA burst frequency and mean RR intervals. The correlation with the normalized value; the MSNA burst incidence (shown by the figure on the right), is lost.



Muscle sympathetic nerve activity showed a significant inverse correlation with mean RR intervals. Because burst activity is closely connected to cardiac cycles, in cases where the incidence approaches 100% of the cycles, burst frequency parallels heart rate. It seems that in spite of the equivalent beta-blocker doses, less effective heart rate control has been achieved in the HFrEF group. Heart rate by itself, however, is not the sole reason for increased burst frequency. The burst incidence, a heart rate-independent parameter, was also abnormally elevated in this group, which clearly indicates the presence of other factors. According to previous studies, sympathetic dysregulation in HFrEF is the result of a diverse mechanism, including blunted arterial baroreflex responses, exacerbated cardiac sympathetic afferent reflexes, chemoreflexes, and paradoxical cardiopulmonary reflexes.[16,27] The contribution of these factors to the increased sympathetic activity in HFmrEF patients is the subject of further studies.[16]

Although the studied HF subgroups were categorized along the arbitrary EF cut-off values, the HF populations could also be characterized by numerous additional functional and laboratory parameters. Among these features, the relationship

Figure 4 MSNA burst frequency and burst incidence in the HFrEF and HFmrEF groups according to the aetiology of heart failure. Values represent mean ± SD.



between the patients' functional state, (NYHA classes) and their sympathetic overactivity has been addressed by numerous studies, with the focus on the sickest population. Results on the mild heart failure group are scarce, and publications sometimes refer to 'merged' NYHA cohorts. The overlap may obscure the differences; nevertheless, a recent meta-analysis found significant elevation in sympathetic activity from mild (NYHA I–II) to severe (NYHA III–IV) heart failure.[28] Our current results are in line with their observation. According to published data, the relationship between ejection fraction and sympathetic activity in heart failure is modest at best. The recent meta-analysis by Grassi *et al*. reaffirms this weak correlation,[28] and our current results provide further evidence. Abnormal 6MWT, which was more frequent in HFrEF patients in our study, was associated with increased sympathetic burst frequency. Incapacitation resulting in inactivity, in itself could contribute to sympathetic activation. The stroke volume index in the whole patient population showed a weak inverse correlation with MSNA burst frequency. An inverse correlation between pulse pressure and MSNA burst frequency might have clinical significance. The complex relationship between pulse pressure and disease progression has been recently described in a large heart failure data base by Teng *et al*.[29] They found that abnormally reduced pulse pressure, which supposedly reflected reduced stroke volume, was significantly associated with mortality in the HFrEF subgroup.[29]

NT-proBNP level has been known to predict prognosis among HFrEF patients. A previous report indicates that its prognostic value is even stronger in HFmrEF; however, certain frequent co-morbidities in this group, that is, diabetes, obesity, and atrial fibrillation may contribute directly to the changes of this marker.[4] Because patients with diabetes and atrial fibrillation were excluded from our study, the strong

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positive correlation between MSNA and NT-proBNP was not related to these conditions.

The aetiology of heart failure may have an impact on the course of the disease and also on autonomic activity. The incidences of ischaemic origin in the HFmrEF and HFrEF subgroups are similar.[20] The evidence regarding the role of aetiology is still conflicting. Grassi *et al*. studied 42 patients with HFrEF and reported no significant difference in the MSNA of ischaemic and non-ischaemic subjects.[19] Notarius *et al*., on the other hand, studied similar, although somewhat younger HFrEF subjects (n = 30) and found significantly increased burst activity in ischaemic heart failure subjects compared with non-ischaemic patients.[18] The differences were attributed by the authors to potentially ongoing ischaemic stimuli.[18] Our current findings on 56 heart failure subjects are in line with Grassi *et al*. The hypothesis forwarded by Notarius *et al*. is not incompatible with our results. No patient with crescendo angina or symptoms that prompted an ED visit during the months prior to the MSNA measurements has been recruited to our study. The lack of apparent ongoing ischaemia may explain the differences. It is important that the same relationship was found when restricting the comparison with the HFmrEF or the HFrEF populations.

Limitations

A limitation of our study is the low number of female participants that precluded subgroup analysis according to gender. Published data on the role of gender in sympathetic activation are limited. Another limitation is that no HFpEF patients were included in our study. Our primary goal was, however, to gather sufficient data to characterize patients in the new HFmrEF category and contrast the findings with the data of the HFrEF population, with which it shares several clinical features.

Conclusions

Our study indicates that within a large cohort of patients with left ventricular systolic dysfunction, the HFmrEF category delineates a group where sympathetic activity is significantly elevated compared with normal; however, significantly less than in the group of HFrEF. HFmrEF patients also belonged to better functional classes, had a higher incidence of preserved exercise capacity, and showed significantly less elevation in their NT-proBNP levels. Our study provides the first evidence that in HFmrEF patients the ischaemic versus non-ischaemic aetiology does not influence sympathetic activation. Our results confirm the same association in the HFrEF group.

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Conflict of interest

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. The corresponding author hereby declares that no figures, tables, or large amounts of text have been included in our manuscript from previous publications. The authors report no conflicts of interest.

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