**Review: The critical deleterious cardiac effects of the sympathetic nervous system in congestive heart failure and a novel new therapeutic approach for correction**

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**ABSTRACT**

**Introduction**. Congestive Heart Failure (CHF) affects 2% of adults. Approximately 50% die within 5 years. The initial adaptive response is increased Sympathetic Nervous System (SNS) activity, increasing cardiac output. Norepinephrine (NE) mediates this by stimulating the β1 adrenergic receptor’s Protein Kinase A (PKA) pathway, increasing activity of: (1) the Sino-Atrial Node (SAN, +chronotropy); (2) L-type Ca++ channels (+inotropy); (3) sarcoplasmic reticulum (SR) ryanodine receptors (RyRs, +inotropy); (4) Ca++-ATPase (SERCA) (+lusitropy); and (5) cardiac myosin-binding protein C (cMyBP-C) (+inotropy/lusitropy). Chronically high SNS tone becomes maladaptive, worsening CHF via desensitization and internalization of β1 receptors, ά1 receptor increased afterload, left ventricular hypertrophy (LVH), changing phosphodiesterase (PDE) isoforms. and necrosis and apoptosis. β-blockade is the cornerstone of therapy. **Focus**. Since CHF mortality and morbidity remain high, we investigated ranolazine’s (RAN) efficacy when added to Guideline therapy. In the first investigation, 54 CHF patients were randomized to adjunctive RAN (RANCHF, 1000mg bid) verses NORANCHF. Autonomic measurements (ANX 3.0 Autonomic Monitor) were taken at baseline and 1 year. Of the entire cohort, 59% were initially abnormal, including high Sympathovagal Balance (SB) that normalized in 10/12 (83%) RANCHF patients verses 2/11 (18%) NORANCHF patients. High SB developed in 5/11 (45%) NORANCHF verses 1/11(9%) RANCHF patients. In the second investigation, matched CHF patients were given adjunctive RAN (1000 mg po-bid) (RANCHF, 41 systolic, 13 diastolic) verses NORANCHF (43 systolic, 12 diastolic). Echocardiographic LVEF and autonomic measures were obtained at baseline and follow-up (mean 23.7 months). LVEF increased in 70% of RANCHF patients, an average of 11.3 units. Mean LVEF remained unchanged in NORANCHF patients. At baseline, 28% of patients had high SB. RAN normalized SB in >50%; the NORANCHF group had a 20% increase in patients with high SB. RAN reduced (composite endpoint) CHF admissions, cardiac death, ventricular tachycardia and fibrillation [VT/VF]) by 40%. **Conclusion**, RAN substantially corrects the maladaptive SNS CHF response.

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**INTRODUCTION**

Congestive Heart Failure (CHF) is a condition when the heart is incapable of satisfying the body’s blood flow needs. CHF is common (2% of adults [1]), costly (the leading cause of hospitalization of older adults [2]), and deadly (35% of patients die within the first year of diagnosis). CHF mortality is similar to some cancers [3,4]. As the population ages, well over 40 million people will be diagnosed globally [5].

This review will detail the increased Sympathetic Nervous System’s (SNS) response, traditionally treated with beta blockers, to CHF and will also suggest a novel new pharmacologic agent, Ranolazine, that effectively and safely improved SNS function, left ventricular ejection fraction (LVEF), and CHF outcomes in our two studies.

**ACTIVATION OF THE SYMPATHETIC NERVOUS SSYSTEM IN CHF**

CHF decreases the inhibitory inputs of the carotid sinus and aortic arch baroreceptors as well as the cardiopulmonary mechanoreceptors. Vagal baroreceptor activity decreases. Excitatory inputs from peripheral chemoreceptors and muscle mechanoreceptors increase [6]. As a result, SNS output increases, and plasma levels of norepinephrine (NE) can be 2 to 3 times normal, increasing α2-activity and afterload, left ventricular hypertrophy (LVH), and are predictive of mortality [7,8]. NE stimulates the cardiac β1-receptor (β1-AR), activating the Protein Kinase A (PKA) pathway [8]. These changes are the same whether the CHF is systolic (HFrEF) or diastolic (HFpEF).

**THE CATECHOLAMINE PROTEIN KINASE A** **PATHWAY**

Catecholamines bind to the transmembrane G-coupled β1-AR, activating adenylyl cyclase (AC) which converts ATP into cAMP rapidly. The cAMP binds the PKA-R subunit, leading to release of free PKA-C subunits, and activation of PKA occurs. Anchoring proteins bind PKA to the L-type Ca++ channel (LTCC, Cav 1.2) and to both the sarcoplasmic reticulum and sarcoendoplasmic reticulum Ca++  - ATPase (SERCA) [8]. PKA binding to the LTCC increases systolic Ca++  entry. PKA binding to the sarcoplasmic reticulum enhances the activities of ryanodine receptors (Ry Rs ), including Ca++ -mediated Ca++  release, which has a +inotropic effect. PKA binding to the SERCA increases Ca++  reuptake, which has a +lusitropic effect. PKA also phosphorylates Phospholamban (PLN), increasing SERCA activity and contributing to + chronotropy [9,10]. PKA phosphorylation of cardiac myosin-binding protein C (cMyBP-C) weakens inhibition of myosin, increasing force-producing myosin heads, and accelerating cross-bridge cycling, resulting in both a +inotropy and +lusitropy [11-14].

**THE CATECHOLAMINE PROTEIN KINASE A** **PATHWAY IN CHF**

Chronically stimulated β1-ARs are downregulated by β1-arrestin-mediated internalization and desensitized by uncoupling from G-proteins. This reduces the SNS’s ability to increase LV contractility (+ inotropy) and improves diastolic dysfunction and Titin compliance (+lusitropy) via catecholamine activation of PKA, thereby exacerbating CHF (8,15). Chronic LTCC activation, resulting in Ca++ -overload, causes myocardial necrosis (increased intracellular Ca++ from any cause results in activation of the mitochondrial death pathway) [8]. Constitutive PKA activation hyperphosphorylates RyR2 and PLN, increasing intracellular Ca++, reducing inotropy and lusitropy. Hyperphosphorylation of RyR2 results in diastolic Ca++-leak, depleting SR Ca++, and causing diastolic contractions. Constitutive PKA activation may also eventuate in a dilated cardiomyopathy and sudden death [16]. PKA’s interaction with its anchoring proteins is reduced in CHF, and anchoring proteins are down-regulated [17,18].

CHF also alters phosphodiesterase (PDE) isoforms. PDE is the enzyme that converts c-ATP to AMP. Decreased PDE3A and PDE4D triggers a SR Ca++-leak, contributing to cytosolic Ca++-overload, arrhythmia-provoking afterpotentials, and apoptosis [8,19,20]. Increased PDE1C, PDE2, and PDE10A reduces cAMP and contractility (-inotropy). Increased β1-AR activity also reduces PKA signaling [8,21,23]. Expressed simply, acute PKA stimulation improves CHF, while chronic stimulation worsens it.

**SYMPATHETIC GANGLIA NEURONAL SODIUM CHANNEL 1.7 (NAV 1.7) AND RANOLAZINE (RAN)**

Nav 1.7 is blocked in its open state in a strongly use-dependent manner by RAN via the local anesthetic receptor [24,25]. Therefore, RAN’s reduction of SNS β1-AR stimulation should increase as SNS tone increases. We administered RAN (1000mg, po, bid) to 30 subjects without CHF or an indication for RAN who had “CHF-like” high SB (>2.5) (see Table 1) [26]. On the fifth day of treatment, ANS responses as measured with the ANX 3.0 Autonomic Monitor improved in 27/30 of the subjects (90%), high SB normalizing in 20/30 subjects (67%) due to decreased SNS tone. After discontinuing RAN, SB returned to baseline levels.

**TABLE 1**: Changes in abnormal Parasympathetic and Sympathetic responses in 30 patients without CHF or angina.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **preRAN** | **postRAN** | **p** |
| **Rest** | **(Mean±SD)** | **(Mean±SD)** |  |
| **LFa** | 3.90 ± 7.88 | 1.44 ± 2.20 | <0.001 |
| **RFa** | 0.81 ± 1.62 | 0.82 ± 1.48 | 0.493 |
| **SB** | 4.53 ± 1.85 | 2.01 ± 1.12 | <0.001 |
| **Deep Breathing** |
| **RFa** | 20.1 ± 47.9 | 26.1 ± 30.4 | 0.553 |
| **E/I** | 1.13 ± 0.10 | 1.14 ± 0.14 | 0.679 |
| **Valsalva** |
| **LFa** | 32.6 ± 47.9 | 30.4 ± 33.3 | 0.700 |
| **VR** | 1.26 ± 0.26 | 1.22 ± 0.24 | 0.130 |
| **Head-up Postural Change (Stand)** |
| **LFa** | 4.27 ± 8.95 | 1.61 ± 2.29 | 0.006 |
| **RFa** | 1.46 ± 3.89 | 0.45 ± 0.75 | 0.139 |
| **30:15** | 1.14 ± 0.13 | 1.16 ± 0.19 | 0.919 |

30:15 = (Stand) 30:15 ratio (unitless); E/I ratio (deep breathing) exhalation/inhalation ratio (unitless); LFa = Low-Frequency area = Sympathetic activity (bpm2); RAN = Ranolazine; RFa = Respiratory Frequency area = Parasympathetic activity (bpm2); SB = Sympathovagal Balance = LFa/RFa (unitless); SD = standard deviation; VR = Valsalva ratio (unitless).

**TABLE 2**: Demographics

|  |  |  |
| --- | --- | --- |
|  | **RANCHF**(n=27) | **NORANCHF**(n=27) |
| **Age (yrs, mean and [range])** | 65 (23-82) | 63 (31-87) |
| **Gender (F, M)** | 10, 17 | 11, 16 |
| **DM2** | 18 (67%) | 17 (63%) |
| **CAD** | 16 (59%) | 17 (63%) |
| **HTN** | 14 (52%) | 13 (48%) |
| **CRD** | 7 (26%) | 4 (15%) |
| **Beta-blocker** | 27 (100%)\* | 26 (96%)\*\* |
| **ACE-I or ARB** | 19 (70%) | 19 (70%) |
| **Statin** | 18 (67%) | 15 (56%) |
| **Aldosterone antagonist** | 13 (48%) | 17 (63%) |
| **BiV-PCD or PCD** | 12 (44%) | 10 (37%) |
| **2D Echo (#: sys, dia)** | 14 (52%)13 (48%) | 15 (56%)12 (44%) |
| **LVEF (mean %: sys, dia)** | 28,58 | 30,52 |
| **LVEF(ranges: sys, dia)** | (18-39) (42-70) | (20-35)(43-68) |

**TABLE 2**: Demographics (con’t)

|  |  |  |
| --- | --- | --- |
|  | **RANCHF**(n=27) | **NORANCHF**(n=27) |
| **LVEDD (mm: sys, dia)** | 62,46 | 59,50 |
| **LVEDD (ranges: sys, dia)** | (52-68) (33-56) | (49-78)(31-63) |
| **LAD (mm) (range)** | 4.57(2.7-6.1) | 4.53(3.3-5.9) |
| **CI (l/in/m², mean: sys, dia)** | 2.30, 2.41 | 2.76, 2.46 |
| **SI (l/in/m², mean: sys, dia)** | 0.40, 0.35 | 0.39, 0.35 |

\*Mean, daily dose = 35 mg Carvedilol or 108 mg Metoprolol.

\*\*Mean, daily dose = 41 mg Carvedilol or 225 mg Metoprolol (92% prescribed Carvedilol).

2D Echo(#: sys, dia) = Two-dimensional echocardiogram, number of patients with systolic or diastolic CHF as determined by 2D Echo; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BiV PCD = bi-ventricular pacing cardiac defibrillator; CAD = Coronary Artery Disease; CHF = congestive heart failure; CI = cardiac index by Bio-Z; dia = diastolic CHF; CRD = Chronic Renal Disease; DM2 = type 2 Diabetes Mellitus; HTN = Hypertension; LAD = left atrial diameter; LVEDD = left ventricular end diastolic diameter; LVEF (mean %: sys, dia) = left ventricular ejection fraction, mean LVEF as a percent for systolic and diastolic subpopulations, respectively, mean sys, dia = mean results for systolic and diastolic subpopulations, respectively; NORANCHF = CHF patients NOT prescribed Ranolazine; RANCHF = CHF patients prescribed Ranolazine; ranges: sys, systolic and diastolic subpopulations, respectively; SI = stroke index; sys = systolic CHF.

**TABLE 3**: Changes in abnormal P&S measures in RANCHF vs. NORANCHF patients.

|  |  |  |
| --- | --- | --- |
| **P&S****(M ± SD)** | **RANCHF****(n = 16)** | **NORANCHF****(n = 16)** |
|  | **preRAN** | **12 months** | **p** | **Initial** | **12 months** | **p** |
| **Rest** |  |  |  |  |  |  |
|  **LFa** | 7.80 ± 15.6 | 0.88 ± 1.18 | 0.034 | 3.65 ± 4.64 | 2.35 ± 2.55 | 0.056 |
|  **RFa** | 0.55 ± 0.95 | 0.50 ± 0.71 | 0.004 | 0.40 ± 0.49 | 0.38 ± 0.52 | 0.086 |
|  **SB** | 15.9 ± 40.71 | 1.90 ± 0.98 | 0.033 | 7.02 ± 5.89 | 8.27 ± 6.33 | 0.132 |
| **Deep breathing** |  |  |  |  |  |
|  **RFa** | 17.3 ± 24.3 | 6.08 ± 4.40 | 0.756 | 11.9 ± 12.5 | 30.0 ± 4.18 | 0.187 |
|  **E/I ratio** | 1.08 ± 0.06 | 1.09 ± 0.08 | 0.198 | 1.10 ± 0.09 | 1.20 ± 0.24 | 0.285 |
| **Valsalva** |  |  |  |  |  |  |
|  **LFa** | 13.2 ± 11.6 | 10.3 ± 12.3 | 0.254 | 12.2 ± 18.0 | 17.3 ± 25.8 | 0.272 |
|  **VR** | 1.17 ± 0.42 | 1.15 ± 0.11 | 0.134 | 1.17 ± 0.22 | 1.17 ± 0.17 | 0.120 |
| **Head-up postural change (stand)** |  |  |  |  |
|  **LFa** | 4.12 ± 13.7 | 0.67 ± 0.97 | 0.071 | 1.90 ± 2.68 | 1.16 ± 1.20 | 0.485 |
|  **RFa** | 1.85 ± 5.83 | 0.17 ± 0.15 | 0.208 | 0.88 ± 0.82 | 1.03 ± 0.87 | 0.049 |
|  **30:15** | 1.15 ± 0.27 | 1.10 ± 0.09 | 0.245 | 1.17 ± 0.15 | 1.12 ± 0.12 | 0.269 |

12 mo = 12-month follow-up; 30:15 = (Stand) 30:15 ratio (unitless); E/I ratio (deep breathing) exhalation/inhalation ratio (unitless); LFa = low-frequency area = sympathetic activity (bpm2); M = mean; P&S = parasympathetic and sympathetic measures; NORANCHF = Congestive Heart Failure patients Not prescribed Ranolazine; RANCHF = Congestive Heart Failure patients prescribed Ranolazine; RFa = respiratory frequency area = parasympathetic activity (bpm2);SB = Sympathovagal Balance = LFa/RFa; SD = standard deviation; VR = Valsalva ratio (unitless).

**RANOLAZINE AND CHF**

Fifty-four (54) Guideline-treated CHF patients were randomized to: (1) open-label RAN (RANCHF) added to usual therapy verses (2) usual therapy (NORANCHF) (Table 2) [26]. P&S measurements were taken at baseline and at 12 months. Baseline P&S measures were abnormal in 59% of patients in each group (Table 3).

Ninety-eight percent (98%) of patients were on a maximum tolerated dose of beta-blocker. The finding that 23/54 (43%) of the CHF patients’ baseline P&S responses demonstrated high SB is consistent with the prevalence of adrenergic escape in systolic CHF cited in a 415-patient study [27]. RAN improved abnormal P&S measures in our CHF patients, including an average 88% reduction in SB (Table 3, p = 0.0330), and SB normalized in 10/12 (83%) of baseline high SB RANCHF patients, once again as a result of reduced SNS tone.

In our second study to evaluate RAN’s effect upon LVEF [28], matched CHF patients (Table 4) were given open-label RAN (1000 mg po-bid) added to guideline-driven therapy (RANCHF, 41 systolic, 13 diastolic) or no adjuvant therapy (control, NORANCHF, 43 systolic, 12 diastolic). Echocardiographic LVEF and P&S measures were obtained at baseline and follow-up (mean 23.7 months). LVEF increased in 70% of RANCHF patients, an average of 11.3 units (Tables 5 & 6). Mean LVEF remained unchanged in NORANCHF patients. At baseline, 28% of patients had high SB; RAN normalized SB in over 50% of these, once again by decreasing SNS tone; in contrast, the NORANCHF group had a 20% increase in patients with high SB (Table 7). RAN reduced MACE by 40%; sudden death by 5.6% vs 12.77%; VT/VF by 11.1% vs 25.6%; CHF admission by 22.2% vs 27.3%.

Although improvements in LVEF and outcomes correlated with reduction of SNS tone, RAN has a second, independent method of action that improves LVEF and outcomes. By binding to amino acid F1760 of the cardiac sodium channel 1.5 (Nav  1.5), RAN reduces the late sodium current (INa  ) present in CHF. INa causes an increase in cardiomyocyte Ca++, resulting in -lusitropy, -inotropy, and early as well as delayed afterpotentials (EADs/DADs) that trigger VT/VF [28].

**CONCLUSIONS**

CHF is common, increasing in prevalence as the population ages, progressive, and still carries an extremely poor prognosis. A major cause of the downward spiral of CHF is chronic SNS activation, so beta blockade has been the cornerstone of pharmacotherapy.

Our studies demonstrate frequently insufficient treatment of the SNS excess in Guideline managed patients that can be addressed by adding Ranolazine. Using currently available technology that measures SNS tone, we can and must identify CHF-treated patients who remain at high risk and adjust therapy when necessary.

**TABLE 4**: Patient demographics

|  |  |  |
| --- | --- | --- |
| **Demographic****(% pop.)** | **Systolic CHF****(LVEF <0.40)** | **Diastolic CHF****(LVEF ≥0.40)** |
|  | **RAN****(N = 41)** | **NORAN****(N = 43)** | **RAN****(N = 13)** | **NORAN****(N = 12)** |
| **Age (mean)** | 61 | 63 | 67 | 63 |
| **Gender****(F, M)** | 20, 21(48.8%, 51.2%) | 28, 15(44.4%, 55.6%) | 5, 8(38.5%, 61.5%) | 6, 6(50.0%, 50.0%) |
| **Comorbidities** |  |  |  |  |
|  **CAD** | 21 (51.2%) | 24 (55.8%) | 7 (53.8%) | 6 (50.0%) |
|  **Diabetes II** | 14 (34.1%) | 12 (27.9%) | 5 (38.5%) | 5 (41.7%) |
|  **Hypertension** | 20 (48.8%) | 24 (55.8%) | 13 (100%) | 9 (75.0%) |
|  **CRD** | 6 (14.6%) | 4 (9.3%) | 3 (23.1%) | 0 |
| **Therapy** |  |  |  |  |
|  **Amiodarone** | 7 (17.1%) | 5 (11.6%) | 0 | 0 |
|  **Beta-blocker** | 40 (97.6%) | 42 (97.7%) | 13 (100%) | 12 (100%) |
|  **Carvedilol** **(ave mg/d)** | 34 | 42 | 34 | 49 |
|  **Metoprolol** **(ave mg/d)** | 100 | 200 | 133 | 200 |
|  **BiV PCD** | 14 (34.1%) | 16 (37.2%) | 0 | 0 |
|  **PCD** | 5 (12.2%) | 3 (7.0%) | 0 | 0 |
|  **ACE-I** | 33 (80.5%) | 38 (88.4%) | 9 (69.2%) | 0 |
|  **Aldosterone Ant.** | 23 (56.1%) | 18 (41.9%) | 7 (53.8%) | 4 (33.3%) |
| **Follow-up (ave. months)** | 24.0 | 20.2 | 25.0 | 25.5 |
| **NYHA Class** | **2** | **3** | **4** |  |
| **RAN syst** | 15 (36.0%) | 23 (56.0%) | 3 (7.0%) |  |
| **RAN dias** | 8 (62.0%) | 5 (38.0%) | 0 |  |
| **NORAN syst** | 19 (44.0%) | 21 (49.0%) | 3 (7.0%) |  |
| **NORAN dias** | 9 (75.0%) | 3 (25.0%) | 0 |  |

ACE-I = angiotensin-converting enzyme inhibitor; Ant = antagonist; ave = average; BiV PCD = bi-ventricular pacing cardiac defibrillator; CAD = coronary artery disease; CHF = congestive heart failure; CRD = chronic renal disease; dias = diastolic; mg/d = milligrams per day; NORAN = no Ranolazine; NYHA = New York Heart Association; PCD = pacing cardiac defibrillator; RAN = Ranolazine; syst = systolic.

**TABLE 5**: Changes in LVEF

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **ΔEFU ≤−7** | **-6≤ΔEFU ≤+6** | **ΔEFU ≥+7** | **p** |
| **RANCHF(N = 54)** | 1 (2%) | 27 (50%) | 26 (48%) | <0.001 |
| **NORANCHF(N = 55)** | 8 (15%) | 43 (78%) | 4 (7%) | <0.001 |

Δ = change; CHF = congestive heart failure; EFU = ejection fraction units; LVEF =left ventricular ejection fraction; NORANCHF = CHF patients not prescribed Ranolazine; RANCHF = CHF patients prescribed Ranolazine.

**TABLE 6**: Echocardiographic results

|  |  |  |
| --- | --- | --- |
|  | **Systolic CHF** | **Diastolic CHF** |
|  | **RAN (N = 41)** | **NORAN (N = 43)** | **RAN (N = 13)** | **NORAN (N = 12)** |
| **LVIDd (ave± SD, cm)** |  |  |  |
| **Initial** | 5.88 ± 0.82 | 6.09 ± 0.74 | 5.16 ± 0.71 | 5.28 ± 0.83 |
| **Final** | 5.84 ± 0.82 | 6.11 ± 0.77 | 5.26 ± 0.46 | 5.47 ± 0.95 |
| **Δp** | 0.679 | 0.831 | 0.543 | 0.637 |
| **LAD (ave±SD, cm)** |  |  |  |
| **Initial** | 4.59 ± 0.73 | 4.51 ± 0.67 | 4.20 ± 0.88 | 4.11 ± 0.65 |
| **Final** | 4.33 ± 0.64 | 4.44 ± 0.62 | 4.30 ± 0.71 | 4.28 ± 0.54 |
| **Δp** | 0.084 | 0.821 | 0.785 | 0.504 |
| **LVIDs (ave±SD, cm)** |  |  |  |
| **Initial** | 4.94 ± 0.81 | 5.21 ± 0.63 | 4.08 ± 0.64 | 4.03 ± 0.67 |
| **Final** | 4.70 ± 0.85 | 5.11 ± 0.77 | 4.00 ± 0.84 | 4.36 ± 0.99 |
| **Δp** | 0.245 | 0.924 | 0.882 | 0.346 |
| **LVEF (ave±SD, %)** |  |  |  |
| **Initial** | 30.46 ± 5.66 | 30.17 ± 5.68 | 42.83 ± 3.46 | 47.50 ± 5.94 |
| **Final** | 36.83 ± 9.97 | 29.20 ± 7.27\*\* | 52.33 ± 8.59 | 47.00 ± 9.35 |
| **Δp** | 0.018 | 0.586 | 0.002 | 0.875 |

CHF = congestive heart failure; LAD = left atrial diameter; LVEF = left ventricular ejection fraction; LVIDd = left ventricular internal diameter diastole; LVIDs = left ventricular internal diameter systole; NORAN = no Ranolazine; Δp = significance of change from initial to final; RAN = Ranolazine; \*p<0.001; \*\*p = 0.013.

**TABLE 7**: Baseline and follow-up P&S measures and LVEF from age-, gender-, and history-matched, arrhythmia-free patients: RANCHF vs. NORANCHF.

|  |  |  |
| --- | --- | --- |
|  | **RANCHF (N = 46)** | **NORANCHF (N = 49)** |
|  | **Initial** | **Final** | **p** | **Initial** | **Final** | **p** |
| **Rest** |  |  |  |  |  |  |
|  **LFa** | 4.91 | 2.49 | 0.034 | 1.74 | 3.42 | 0.015 |
|  **RFa** | 1.64 | 1.56 | 0.047 | 0.70 | 0.93 | 0.012 |
|  **SB** | 2.42 | 1.98 | 0.019 | 2.61 | 4.28 | 0.039 |
| **Deep breathing** |  |  |  |  |  |
|  **RFa** | 15.8 | 13.7 | 0.065 | 7.66 | 11.8 | .267 |
|  **E/I ratio** | 1.11 | 1.09 | 0.552 | 1.11 | 1.11 | 0.156 |
| **Valsalva** |  |  |  |  |  |  |
|  **LFa** | 35.6 | 29.0 | 0.050 | 17.8 | 11.8 | 0.187 |
|  **VR** | 1.20 | 1.24 | 0.359 | 1.17 | 1.19 | 0.753 |
| **Head-up postural change challenge (Stand)** |  |  |  |  |
|  **LFa** | 2.63 | 2.13 | 0.006 | 2.83 | 1.28 | 0.011 |
|  **RFa** | 2.20 | 0.76 | 0.002 | 0.82 | 0.90 | 0.011 |
|  **30:15 ratio** | 1.16 | 1.09 | 0.075 | 1.16 | 1.17 | 0.068 |

bpm2 = beats per min2; EFU = ejection fraction unit; E/I ratio = exhalation to inhalation ratio (unitless); LFa = low-frequency area (bpm2), a measure of sympathetic activity; LVEF = left ventricular ejection fraction; RAN = Ranolazine: RANCHF = congestive heart failure patients treated with RAN; RFa = respiratory frequency area (bpm2), a measure of parasympathetic activity; SB = Sympathovagal Balance (unitless); VR = Valsalva ratio (unitless); 30:15 ratio = ratio of 30th to the 15th R-R interval immediately after standing (unitless).

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