

Ranolazine improves autonomic balance in heart failure when added to guideline-driven therapy

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ABSTRACT

Background: The effect of ranolazine (RAN) on cardiac autonomic balance in congestive heart failure (CHF) was studied.

Methods: Fifty-four CHF patients were randomized to (1) open-label RAN (RANCHF) added to usual therapy vs. (2) usual therapy (NORANCHF). Parasympathetic and sympathetic (P&S) measurements were taken at baseline and at 12 months.

Results: A total of 16/27 (59%) patients in both groups had initially abnormal P&S measures, including high sympathovagal balance (SB), cardiovascular autonomic neuropathy (CAN) or both. High SB normalized in 10/12 (83%) RANCHF patients vs. 2/11 (18%) NORANCHF patients. SB became high in 5/11 (45%) NORANCHF vs. 1/11 (9%) RANCHF patients. CAN improved in 4/6 (67%) RANCHF patients vs. 5/7 (45%) NORANCHF patients. CAN developed in 1/11 (9%) RANCHF vs. 4/11 (36%) NORANCHF patients. Since improved P&S in RANCHF patients seemed independent of improved brain natriuretic peptide and impedance cardiography (BioZ) measurements, 5 day RAN was given to 30 subjects without CHF but with high SB or CAN. P&S improved in 90% of these subjects.

Conclusions: RAN improves unfavorable P&S activity in CHF possibly by a direct effect upon autonomic sodium channels.

Keywords: Cardiovascular autonomic neuropathy, Congestive heart failure, Major adverse cardiac events, Parasympathetic function, Patient outcomes, Ranolazine, Sympathetic function

Introduction

In congestive heart failure (CHF), there is an increase in the myocardial late sodium current (I_{Na}) leading to an intracellular calcium (Ca^{++}) overload that causes diastolic dysfunction, microvascular ischemia and early after-depolarizations, increasing the risk of sudden death. In therapeutic concentrations, ranolazine (RAN) decreases the rate of I_{Na} by 50%, thereby improving this Ca^{++} -related mechanical and electrical dysfunction (1). Therefore, RAN potentially could improve the mechanical and electrical dysfunction of CHF. Since neuronal sodium channel 1.7 ($Na_{v1.7}$) is blocked in its open state in a strongly use-dependent manner by RAN at therapeutic concentrations (2-6 μ M) via the local anesthetic receptor (2, 3),

it is possible that RAN can directly alter the function of the parasympathetic and sympathetic (P&S) branches of the autonomic nervous system (ANS). Consequently, an additional potential benefit of RAN in CHF could be improvement in the damaging autonomic dysfunction that it accompanies. This is the first study on changes in P&S measures in CHF patients treated with RAN added to guideline-driven therapy.

Methods

In 2006, 54 patients treated for CHF according to ACC/AHA guidelines (4) were randomized to (1) open-label RAN added to usual care (RANCHF, $n = 27$) or (2) continued usual care (NORANCHF, $n = 27$) (Tab. I). Since patients were on maximally tolerated doses of beta-blockers and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), only the diuretic dose was adjusted if needed. Diastolic CHF was defined as CHF with a left ventricular ejection fraction (LVEF) ≥ 0.40 . At baseline, 2D echocardiograms, impedance cardiograms (BioZ, Cardio Dynamics, San Diego, CA) and brain natriuretic peptides (BNPs) were obtained. P&S function was assessed noninvasively using the ANSAR Medical Technologies, Inc. (Philadelphia, PA) software (ANX 3.0 autonomic function monitor) which computes simultaneous, independent measures of P&S activity (P&S monitoring) based on continuous,

Accepted: July 25, 2014

Published online: September 23, 2014

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TABLE I - Demographics

| Demographic | RANCHF (n = 27) | NORANCHF (n = 27) |
|--|----------------------------|----------------------------|
| Age (yrs, mean and range) | 65 (23-82) | 63 (31-87) |
| Gender (F, M) | 10, 17 | 11, 16 |
| Type 2 diabetes mellitus | 18 (67%) | 17 (63%) |
| Coronary artery disease | 16 (59%) | 17 (63%) |
| Hypertension | 14 (52%) | 13 (48%) |
| Chronic renal disease | 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) (ranges: sys, dia) | 28, 58 (18-39), (42-70) | 30, 52 (20-35), (43-68) |
| LVEDD (mm: sys, dia) (ranges: sys, dia) | 62, 46 (52-68), (33-56) | 59, 50 (49-78), (31-63) |
| LAD (mm) (range) | 4.57 (2.7-6.1) | 4.53 (3.3-5.9) |
| CI (l/in/m ² , mean: sys, dia) | 2.30, 2.41 | 2.76, 2.46 |
| SI (l/in/m ² , 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% of the patients were prescribed Carvedilol).

2D Echo = Two-dimensional echocardiogram; 2D Echo (#: sys, dia) = 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; CHF = congestive heart failure; CI = cardiac index by Bio-Z; dia = diastolic CHF; LAD = left atrial diameter; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; LVEF (mean%: sys, dia) = 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, dia = ranges for systolic and diastolic subpopulations, respectively; SI = stroke index; sys = systolic CHF.

time–frequency analysis of heart rate variability (HRV) with concurrent, time–frequency analysis of continuous respiratory activity (RA). The following variables were recorded: seated resting (5 min) P&S activity (respiratory frequency area (RfA) and low-frequency area (LFa), respectively) was computed from P&S Monitoring (5-9); exhalation/inhalation (E/I) ratio and RfA were computed in response to 1 min of deep breathing (paced breathing at 6 breaths/min) (9); Valsalva ratio and Lfa were computed in response to a series of short Valsalva maneuvers (≤ 15 sec); and BP, Lfa, RfA and 30:15 ratio were computed in response to 5 min of head-up postural change (quick stand followed by 5 min of quiet standing). Sympathovagal balance (SB) is computed as Lfa/RfA (reported means are averages of ratios, not ratio of averages). Cardiac autonomic neuropathy (CAN) was defined in standard fashion (10), reflecting very low para-

sympathetic activity (RfA < 0.1 bpm²). Parasympathetic activity (RfA) was defined as the spectral power within a 0.12 Hz-wide window centered on the fundamental respiratory frequency (FRF) in the HRV spectrum (5-9). FRF was identified from time–frequency analysis of RA. Effectively, FRF is a measure of Vagal outflow, as it effects the heart. Sympathetic activity (LFa) was defined as the remaining spectral power, after computation of RfA, in the low-frequency window (0.04-0.15 Hz) of the HRV spectrum (5-9). This method is valid regardless of challenge or patient state or history. Normal SB is $0.4 < SB < 3.0$. High SB (> 3.0) and CAN define high mortality risk, including silent myocardial infarction and sudden cardiac death (11-14). The 30:15 ratio is the ratio of the 30th R-R interval after a quick head-up postural change (standing) to the 15th R-R interval after standing. The 30:15 ratio reflects the reflex bradycardia upon standing that is dependent upon sympathetic vasoconstriction. The Valsalva ratio is the ratio of the longest R-R interval to the shortest R-R during a 15 sec Valsalva maneuver. The E/I ratio is the ratio of the heart beat interval during peak exhalation over that during peak inhalation during paced breathing. The E/I ratio is a measure of, more or less, Vagal (parasympathetic) tone, as are the 30:15 and Valsalva ratios.

RANCHF patients were prescribed RAN 500-1000 mg bid. P&S, BNPs, and BioZs were repeated in 12 months (echocardiograms were not repeated at this time). When it was noted that P&S activity could change in RANCHF patients independently of BNP and BioZ changes, we identified another 30 subjects without CHF or an indication for RAN (20 male, 10 female, average age 61 years) with “CHF-like” abnormal P&S activity with high SB (25/30, 83%), CAN (1/30, 3%) or both (4/30, 13%). Twenty (67%) had a history of coronary disease, but only 5 (17%) were not completely revascularized, and 3 (10%) had a positive nuclear stress test. Sixteen (53%) were hypertensive, 11 (31%) were diabetic and 4 (13%) were on a beta-blocker. The causes of their abnormal P&S included chronic pain or anxiety, diabetes and hypertension. RAN 500-1000 mg bid was prescribed, and the P&S testing repeated on the 5th day. No subject had high BNP or low LVEF.

All statistics, including means, standard deviations and Student *t*-tests, were performed under SPSS v 14.1. Student *t*-tests were performed as 2-tailed with equal variance. Significance values were determined on the null hypothesis that the pre- and posttreatment P&S values were equal.

Results

Table I lists the demographics of the RANCHF and NORANCHF populations. These two populations were well matched. CHF management guidelines (4) were strictly followed. Almost 100% of the patients were prescribed beta-blockers, 91% of the patients without chronic renal disease were prescribed an ACE inhibitor or ARB and 76% of the systolic CHF patients had defibrillators. Over 60% of these populations are diagnosed with diabetes.

Average changes in abnormal P&S measures in RANCHF vs. NORANCHF patients are presented in Table II. Individually, 16/27 RANCHF patients (59%, including 9 systolic and 7 diastolic CHF patients) had abnormal baseline P&S responses: 10 patients (37%) demonstrated high SB, 4 patients (15%) demonstrated CAN and 2 patients (7%) demonstrated both.



TABLE II - 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). See text for details.

Of the NORANCHF patients, 16/27 (59%) had abnormal baseline P&S responses, 9 patients (33%) demonstrated high SB, 5 patients (19%) demonstrated CAN and 2 patients (7%) demonstrated both. Fifteen of 16 RANCHF patients (94%) with initially abnormal P&S responses improved, and 14/16 patients (88%) normalized high SB and corrected CAN as compared with only 7/16 NORANCHF patients (44%) ($p = 0.0330$). On average (Tab. II), the RANCHF patients demonstrated a significant improvement in SB (from 15.9 to 1.90, $p = 0.0330$), indicating a relative reduction in sympathetic activity. This is not the case for the NORANCHF patients (SB from 7.02 to 8.27, $p = 0.130$), whose SB remained high, indicating a persistent relative, resting sympathetic excess. Only 8/16 NORANCHF patients (50%) with abnormal baseline P&S improved ($p = 0.0560$). Individually, of the NORANCHF patients, only 2/11 (18%) normalized their high SB, as compared with 10/12 RANCHF patients (83%, $p = 0.0130$). Four NORANCHF patients (15%) demonstrated SB responses that became abnormally high during the 12 months of no RAN therapy. Individually, of the NORANCHF patients, 5/7 (71%) corrected their CAN as compared with 4/6 (67%) RANCHF patients. On average (Tab. II), the resting parasympathetic response (RFa) for the RANCHF patients was higher (0.50 bpm²) than that for the NORANCHF patients (0.38 bpm², $p = 0.0040$).

As a control experiment, we investigated changes in initially normal P&S measures in RANCHF vs. NORANCHF patients

(Tab. III). Individually, 11/27 patients (41%) from both RANCHF and NORANCHF populations demonstrated normal, baseline P&S responses. However, only 1/11 RANCHF patients (9%) developed high SB as compared with 5/11 NORANCHF patients (45%, $p = 0.0170$). Similarly, 1/11 RANCHF patients (9%) developed CAN as compared with 4/11 NORANCHF patients (36%, $p = 0.0160$). On average (Tab. III), RANCHF patients demonstrated a decrease in resting, sympathetic activity at 12-month follow-up ($p = 0.0540$) as compared with an increase in the resting, sympathetic activity in the NORANCHF patients ($p = 0.0410$). Conversely (Tab. III), the RANCHF patients demonstrated an increase in resting, parasympathetic activity at 12-month follow-up ($p = 0.0780$) as compared with a decrease in resting, parasympathetic activity in the NORANCHF patients ($p = 0.0160$). The resulting average SB for RANCHF patients decreased ($p = 0.0170$), as compared with an increase in average SB for the NORANCHF patients ($p = 0.0200$).

Changes in BioZ and BNP measures in RANCHF patients with initially abnormal P&S responses are presented in Table IV. The hemodynamic responses to RAN were not uniform. In the initially abnormal P&S response for RANCHF patients, no improvement in BioZs and BNPs was found in 7/17 patients (41%). Importantly, despite this, abnormal P&S responses improved equally well as in the RANCHF patients whose BioZ and BNP responses improved, suggesting a

TABLE III - Changes in normal P&S measures in RANCHF patients

| P&S (M ± SD) | RANCHF (n = 11) | | | NORANCHF (n = 11) | | |
|--|--------------------|-------------|-------|----------------------|-------------|-------|
| | preRAN | 12 months | p | Initial | 12 months | p |
| Rest | | | | | | |
| LFa | 1.32 ± 1.41 | 0.81 ± 0.90 | 0.054 | 0.89 ± 0.73 | 1.09 ± 0.99 | 0.041 |
| RFa | 0.88 ± 0.85 | 1.51 ± 2.10 | 0.078 | 0.63 ± 0.58 | 0.53 ± 0.92 | 0.016 |
| SB | 0.91 ± 0.72 | 0.53 ± 1.34 | 0.017 | 1.51 ± 0.83 | 4.73 ± 4.89 | 0.020 |
| Deep breathing | | | | | | |
| RFa | 13.6 ± 15.2 | 8.51 ± 12.4 | 0.954 | 2.54 ± 3.44 | 9.06 ± 12.1 | 0.066 |
| E/I ratio | 1.13 ± 0.09 | 1.15 ± 0.23 | 0.672 | 1.11 ± 0.13 | 1.09 ± 0.08 | 0.170 |
| Valsalva | | | | | | |
| LFa | 37.7 ± 39.1 | 41.3 ± 64.4 | 0.021 | 9.79 ± 15.1 | 12.1 ± 14.1 | 0.096 |
| VR | 1.25 ± 0.18 | 1.19 ± 0.14 | 0.524 | 1.16 ± 0.11 | 1.16 ± 0.12 | 0.141 |
| Head-up postural change (stand) | | | | | | |
| LFa | 2.49 ± 4.04 | 0.71 ± 0.93 | 0.091 | 1.79 ± 3.50 | 0.87 ± 0.92 | 0.091 |
| RFa | 2.20 ± 3.66 | 0.51 ± 0.91 | 0.590 | 0.97 ± 1.18 | 0.72 ± 0.81 | 0.055 |
| 30:15 | 1.21 ± 0.15 | 1.10 ± 0.09 | 0.704 | 1.15 ± 0.13 | 1.13 ± 0.09 | 0.377 |

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).

TABLE IV - Bio-Z and BNP changes in 16 RANCHF patients with initially abnormal P&S results

| (M ± SD) | Hemodynamically improved (n = 9) | | | Hemodynamically unchanged (n = 7) | | |
|----------|-------------------------------------|-------------|-------|--------------------------------------|-------------|-------|
| | preRAN | 12 months | p | preRAN | 12 months | p |
| CI | 2.14 ± 0.59 | 3.14 ± 0.61 | 0.004 | 2.44 ± 0.89 | 2.40 ± 0.74 | 1.000 |
| SI | 0.30 ± 0.10 | 0.46 ± 0.11 | 0.004 | 0.32 ± 0.15 | 0.31 ± 0.13 | 0.730 |
| BNP | 481 ± 316 | 73 ± 37 | 0.039 | 293 ± 254 | 218 ± 172 | 0.730 |

BNP = brain natriuretic peptide; CI = cardiac index (l/in/m², mean); RANCHF = Congestive Heart Failure patients prescribed RANolazine; SI = stroke index (l/in/m², mean), see Table II for more abbreviations.

possible direct effect on nervous system Na_v channels. To investigate this possibility (Tab. V), 30 subjects without CHF or an indication for RAN who had “CHF-like” high SB or CAN were given RAN. On the 5th day of treatment, P&S responses improved in 27/30 of the subjects (90%), normalizing in 20/30 subjects (67%). Isolated high SB normalized in 16/25 subjects (64%). The one subject with CAN demonstrated an increase in resting parasympathetic activity, relieving the CAN. For 3/4 subjects (75%) demonstrating both high SB and CAN, both P&S measures normalized. After discontinuing RAN, P&S responses returned to baseline levels.

Discussion

The patient populations have significant subpopulations diagnosed with diabetes. This reflects the general population of Memphis, TN, the region of our clinic. It is one of the most obese populations in the United States. While diabetic autonomic neuropathy (DAN) is a well-known precursor to CAN and may affect P&S measures, including SB, P&S measures are similarly effected in patients not diagnosed with diabetes prior to CAN. The precursor to CAN in nondiabetic patients is advanced autonomic dysfunction (AAD). AAD carries the



TABLE V - Changes in abnormal P&S responses in 30 patients without CHF or angina

| | preRAN | Post-RAN | p |
|--|-------------|-------------|---------|
| Rest | | | |
| LFa | 3.90 ± 7.88 | 1.44 ± 2.20 | 0.0001 |
| RFa | 0.81 ± 1.62 | 0.82 ± 1.48 | 0.4930 |
| SB | 4.53 ± 1.85 | 2.01 ± 1.12 | <0.0001 |
| Deep breathing | | | |
| RFa | 20.1 ± 47.9 | 26.1 ± 30.4 | 0.553 |
| E/I ratio | 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); P&S = parasympathetic and sympathetic measures; RFa = respiratory frequency area = parasympathetic activity (bpm²); SB = sympathovagal balance = LFa/RFa; SD = standard deviation; VR = Valsalva ratio (unitless).

same P&S criteria as DAN: abnormally low P&S activity at rest, with $p \geq 0.1$ bpm², with similar symptoms.

RAN affects cardiac Na_v function by binding to Na_v amino acid F1760 (1). The late I_{Na} is reduced by 50%. Since RAN blocks open neuronal Na_v 1.7 in a strongly use-dependent manner via the local anesthetic receptor (2), RAN could have direct effects upon ANS Na_v channels.

High sympathetic activity and CAN have been associated with major adverse cardiac events (MACE), including sudden death (5, 11, 12). Since structural abnormalities also increase MACE (13), baseline 2D echocardiograms were obtained. In our systolic CHF patients, structural findings were consistent with high MACE risk. Mean values for left ventricular end diastolic diameter (Tab. I) and left atrial diameter were 61 mm and 45 mm, respectively. CAN is associated with very low resting parasympathetic activity. In this study, the RANCHF patients demonstrated more parasympathetic activity (Tab. II). More sympathetic activity is known to increase cardiovascular risk (14). More parasympathetic activity at rest is cardioprotective (15). These effects of RAN are borne out in the control patients. The RANCHF control patients demonstrated a decrease in absolute resting sympathetic activity and an increase in absolute resting parasympathetic activity, with a decrease in SB. The converse is true for the NORANCHF patients (Tab. III).

Despite aggressive CHF management, 32/54 (59%) of our CHF patients had initially high SB, CAN or both (Tab. II). Ninety-

eight percent of patients were on a maximum tolerated dose of beta-blocker. 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 recent 415 patient study (16). RAN improved abnormal P&S measures in our CHF patients, including an average 88% reduction in SB (Tab. II, $p = 0.0330$), and SB normalized in 10/12 (83%) of baseline high SB RANCHF patients. CAN improved in 5/7 (71%) of the RANCHF patients.

Although P&S measures change with changing hemodynamics (17-19), RAN was associated with P&S changes even when no definite changes in BNP or BioZ measures were found. Although the mechanism is unknown, a direct effect on nervous system Na_v channels is possible. This is supported by the results in the 30 subjects with "CHF-like" P&S responses who had neither CHF nor an indication for RAN. Five days of RAN improved high SB and CAN in 27/30 (90%), normalizing SB and CAN in 20/30 (67%) of subjects (Tab. V). P&S responses returned to baseline after discontinuing RAN. That P&S function can change independently of hemodynamics has been established. For example, diabetes control (20) and alpha lipoic acid (21) affect P&S and HRV measures. Notably, despite the favorable hemodynamic effects of renin-angiotensin-aldosterone antagonists in CHF, their impact on HRV measures has been mixed (11); however, this may be due to the mixed nature of HRV as a P&S measure calculated from 24-hour Holter monitors.

As expected, hemodynamics did affect P&S function in our CHF patients. On average, cardiac index (CI) was lower in the initially abnormal P&S response group (2.35 l/min/m²) than in the initially normal P&S response group (2.66 l/min/m²). However, resting hemodynamics could not always predict abnormal P&S responses, as NORANCHF patients with initially abnormal P&S responses had higher CI and lower BNPs than RANCHF patients with normal P&S responses (2.55 vs. 2.35 l/min/m² and 293 vs. 480 l/min/m², respectively). That RAN improved hemodynamics more in our diastolic CHF than systolic CHF patients is consistent with RAN's proposed mechanism of action (1), and suggests RAN could impact greatly the dyspnea of diastolic CHF. Our diastolic RANCHF patients (LVEF 41-54%) typically had a ≥ 10 LVEF unit (EFU) increase by 12 months and 45% of RANCHF patients (both systolic and diastolic) increased LVEF by at least 6 EFUs, some doubling their baseline LVEF.

Two RANCHF patients required hospitalization for acute CHF, and another suffered sudden death. There were four acute CHF hospitalizations in the NORANCHF group, along with two sudden deaths. This is consistent with the 1.9 hazard ratio of mortality found in CHF patients with persistently high sympathetic activity despite therapy (16). Prior to hospitalization, P&S measures showed the development of CAN with high SB in the RANCHF patient who died suddenly and in all six NORANCHF patients who were hospitalized for CHF or died of sudden death.

Several of our patients were taking Amiodarone: 5 RAN patients and 4 NORAN patients. There has been some concern regarding concomitant administration since RAN lengthens the QT interval approximately 6 msec. QTc increased 5 msec in the RAN patients. There was no change in QTc in the NORAN patients prescribed Amiodarone. Overall, no patient

demonstrated a QTc >460 msec. Since RAN reduces afterdepolarizations and does not cause transmural dispersion of repolarization, it is unlikely that an adverse drug-drug interaction would occur. On the contrary, in animal experiments, RAN prevented *torsade de pointes* caused by several different antiarrhythmics (22).

Although RAN did not affect BP in angina patients pre-release (23, 24), concomitant with an 88% reduction in SB, standing BP fell an average 5 mmHg in the RANCHF group. Although no patient developed orthostatic symptoms, these patients require close monitoring. Importantly, of the 11 RANCHF patients with initially normal P&S responses, only one developed low SB (Tab. III).

The ANSAR technique of P&S analysis was chosen for two reasons. First, spectral analysis in the ANX-3.0 is based on the time–frequency analysis technique of continuous wavelet transforms (CWT), rather than the frequency-only analysis technique, the fast Fourier transforms (FFTs). Although FFT, including short-term FFTs, is accurate for stationary signals, it causes a compromise between time and frequency resolution due to the fixed length windows used in analysis. The P&S activity monitored during clinical testing, including the Ewing Challenges (25), is from nonstationary, continuous RA and HRV signals. CWT allows adjustment of window length to the features of the signal, resulting in better time–frequency resolution (26). Second, instead of assuming that parasympathetic modulation always lies within the 0.15–0.40 Hz frequency range, P&S monitoring measures parasympathetic modulation based on a second independent measure of the ANS: RA (e.g., via impedance plethysmography). Since respiratory sinus arrhythmia is purely parasympathetic in etiology (6–9), spectral analysis of RA is a measure of the frequency of Vagal input to the heart. This measure has been labeled the FRF (6). For example, if the patient’s respiratory rate (FRF) is very slow, parasympathetic activity would (at least in part) be contained within the low-frequency range of HRV (26). In general, the low-frequency range of HRV is assumed to be sympathetic in nature, even though the low-frequency range of HRV is defined as sympathetic activity as modulated by parasympathetic activity (i.e., respiratory sinus arrhythmia) (27). Therefore, slow respiratory rates leading to higher low-frequency HRV responses would be misinterpreted as increased sympathetic activity unless FRF analysis is done. This example is epitomized in the typical, slow-paced breathing of the Ewing challenge known as deep breathing. The Ewing deep breathing challenge requires that the subject’s breathing is paced at six breaths per minute, or 0.10 Hz. This causes a significant increase in the low-frequency HRV measure with little or no change in the high-frequency HRV measure (26). As with the assumption that the low-frequency HRV measure is purely sympathetic, the high-frequency measure of HRV is assumed to be purely parasympathetic (27). Given the assumption that the low-frequency response is sympathetic, the response to deep breathing would be misinterpreted. With the ANX-3.0, P&S time–frequency ranges are more accurately isolated (5–9, 26).

Since activity in both P&S branches decreases with age and some chronic conditions (28–30), high SB is an indication of (relative) sympathetic excess. Normal SB, in our laboratory, was established from 0.4 to 3.0 (unitless) by studying 260 sub-

jects with no obvious reason for autonomic dysfunction. This range matches that of the manufacturer. That RAN improved CAN is not obvious from the results as presented in Tables II and V. Interpretation of each individual P&S study revealed CAN improvement if present. Since RAN decreased high sympathetic modulation, an increase in parasympathetic modulation would be anticipated due to the “yin yang” nature of the ANS. However, it is likely that RAN directly decreases P&S activity, thereby reducing to some extent the “reflex” increase in parasympathetic activity caused by decreased sympathetic activity.

Limitations

Whether improved P&S measures in CHF patients are a surrogate for reduced risks of sudden death, disease progression and hospitalizations remains to be determined. Toward these ends, preliminary evidence from a 3-year study in our laboratory, focused on echocardiographic changes in 54 RANCHF patients (41 systolic, 13 diastolic) vs. 55 NORANCHF patients (43 systolic, 12 diastolic), revealed that 21/55 (38%) NORANCHF patients had 35 MACE (hospitalized for CHF, had pacing cardiac defibrillator therapy for VT/VF or died), as compared with 17/54 (31%) RANCHF patients having 21 MACE ($p = 0.0614$). Of these 109 patients, 95 were successfully tested for P&S function. RANCHF patients and patients from both groups without MACE had lower SB; the RANCHF group also had higher parasympathetic modulation (RFa).

Conclusions

Despite aggressive guideline-driven therapy in CHF patients, a significant number have unfavorable P&S profiles, even while taking up to 50 mg Carvedilol bid, or 200 mg Metoprolol daily. RAN causes a dramatic improvement in abnormal P&S measures, apparently independent of the CI or BNP responses. This suggests a possible direct effect on autonomic Na_v channel function. RAN blocks neuronal channel $Na_{v1.7}$. Worsening P&S responses appear to predict MACE. Therefore, P&S monitoring could become an important management tool in CHF. Current management of CHF does not include P&S measurements, so that the effect of beta-blockers and ACE inhibitors or ARBs upon the neurohumoral paradigm of CHF in our patients is never quantitated.

Disclosures

Financial support: No grants or funding have been received for this study.

Conflict of interest: Dr. Colombo is a part owner, employee, medical director and executive vice president of ANSAR Medical Technologies, Inc.

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