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

**Gary L. Murray**\(^1\)* and **Joseph Colombo**\(^2,3\)

\(^1\)Director of Clinical Research, The Heart and Vascular Institute, Germantown, TN-USA.

\(^2\)Autonomic Laboratory, Department of Cardiology, Drexel University College of Medicine, Philadelphia – USA

\(^3\)ANSAR Medical Technologies, Inc., Philadelphia – USA

**Published Date**

**February 04, 2020**

Published in the Journal of

**Clinical Cardiology and Cardiovascular Interventions**

**Auctores Publishing, LLC**

16192 Coastal Highway

Lewes, DE 19958,

USA
Ranolazine Improves Autonomic Balance in Heart Failure when added to Guideline-Driven Therapy

Gary L. Murray1*, Joseph Colombo2,3
1The Heart and Vascular Institute, Germantown – USA
2Autonomic Laboratory, Department of Cardiology, Drexel University College of Medicine, Philadelphia – USA
3ANSAR Medical Technologies, Inc., Philadelphia – USA

*Corresponding Author: Gary L. Murray, The Heart and Vascular Institute, Germantown - USA

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 162/7 (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\textsubscript{Na\textsuperscript{L}}) leading to an intra- cellular calcium (Ca\textsuperscript{++}) overload that causes diastolic dysfunction, microvascular ischemia and early after-depolarizations, increasing the risk of sudden death. In therapeutic concern- trations, ranolazine (RAN) decreases the rate of I\textsubscript{Na\textsuperscript{L}} by 50%, thereby improving this Ca\textsuperscript{++}-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\textsubscript{v1.7}) is blocked in its open state in a strongly use-dependent manner by RAN at therapeutic con-centrations (2-6 mM) 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 au-tonomic 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) (Table 1). 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 frac- tion (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 mea- sures of P&S activity (P&S monitoring) based on continuous, 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 LFn/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 bpm^2). 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 affects 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 myo- cardiac 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 stand-ing. The 30:15 ratio reflects the reflex bradycardia upon stand-ing that is dependent upon sympathetic vasoconstriction. The Valsalva ratio is the ratio of the longest R-R interval to the short-est 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.

| 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%) | 12 (44%) |
| LVEF (mean%: sys, dia) | 28, 58 | 30, 52 |
| LVEDD (mm: sys, dia) | (18-39), (42-70) | (20-35), (43-68) |
| LAD (mm: range) | 62, 46 | 59, 50 |
| CI (l/min/m^2, mean: sys, dia) | 2.30, 2.41 | 2.76, 2.46 |
| SI (l/min/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).

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 BNPs 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. Sig-nificance 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 base-line P&S responses; 10 patients (37%) demonstrated high SB, 4 patients (15%) demonstrated CAN and 2 patients (7%) demonstrated both. Of the NORANCHF patients, 16/27 (59%) had abnormal base-line 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 (Table 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 (Table II), the resting parasympathetic response (RFa) for the RANCHF patients was higher (0.50 bpm^2) than that for the NORANCHF patients (0.38 bpm^2, p = 0.0040).

**TABLE II - Changes in abnormal P&S measures in RANCHF vs. NORANCHF patients**

| P&S (M ± SD) | RANCHF | NORANCHF |
|--------------|--------|----------|
|              | (n = 16) | (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.
As a control experiment, we investigated changes in ini- tially normal P&S measures in RANCHF vs. NORANCHF patients (TABLE. 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%) de- veloped high SB as compared with 5/11 NORANCHF patients (45%, p = 0.0170). Similarly, 1/11 RANCHF patients (9%) devel- oped CAN as compared with 4/11 NORANCHF patients (36%, p = 0.0160). On average (TABLE. III), RANCHF patients demon- strated 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 (TABLE. III), the RANCHF patients dem- onstrated 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 de- creased (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 uni- form. 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 pa- tients whose BioZ and BNP responses improved, suggesting a possible direct effect on nervous system NaV channels. To investigate this possibility (TABLE. 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.

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

| P&S (M ± SD) | RANCHF | NORANCHF |
|-------------|--------|---------|
|              | (n = 11) | (n = 11) |
| 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 pre- scribed 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.

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 affected in patients not diagnosed with diabetes prior to CAN. The precursor to CAN in nondiabetic patients is advanced autonomic dysfunction (AAD). AAD carries the same P&S criteria as DAN: abnormally low P&S activity at rest, with p≥0.1 bpm², with similar symptoms.

RAN affects cardiac Na⁺v function by binding to Na⁺v amiloride acid F1760 [1]. The late IₙNa 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 dia-stolic diameter (TABLE. 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 (TABLE. 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 ab-solute resting sympathetic activity and an increase in absolute resting parasympathetic activity, with a decrease in SB. The converse is true for the NORANCHF patients (TABLE. III).

Despite aggressive CHF management, 32/54 (59%) of our CHF patients had initially high SB, CAN or both (TABLE. II). Ninety-eight percent of patients were on a maximum tolerated dose of beta-blocker. That 23/54 (43%) of the CHF patients’ base-line 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% re-duction in SB (TABLE. 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 hemody-namics [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 Nav 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%), normalized SB and CAN in 20/30 (67%) of subjects (TABLE. V). P&S re sponses 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-angio tensin-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 BNP 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 haz- ard ratio of mortality found in CHF patients with persistently high sympathetic activity despite therapy [16]. Prior to hos- pitalization, 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 con- cern regarding concomitant administration since RAN length- ens 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 after- depolarizations and does not cause transmural dispersion of repolarization, it is unlikely that an adverse drug–drug inter- action 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 prere- lease [23, 24], concomitant with an 88% reduction in SB, stand- ing 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 pa- tients with initially normal P&S responses, only one developed low SB (Table. 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 0.15–0.4 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 respi- ratory 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 (bpm2); P&S = parasym pathetic and sympathetic measures; RFa = respiratory frequency area = parasympathetic activity (bpm2); SB = sympathovagal bal- ance = LFa/RFa; SD = standard deviation; VR = Valsalva ratio (unitless).
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 ac–curately 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 subjects 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 sym–pathetic modulation, an increase in parasympathetic modula–tion would be anticipated due to the “yin yang” nature of the ANS. However, it is likely that RAN directly decreases P&S ac–tivity, 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 progres–sion 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 com– pared with 17/54 (31%) RANCHF patients having 21 MACE (p = 0.0614). Of these 109 patients, 95 were successfully test– ed 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 pa–tients, 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 NaV channel function. RAN blocks neuronal channel Nav1.7. 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.

References

1. Shroyck JC, Belardinelli L. (2008) Inhibition of late sodium current to reduce electrical and mechanical dysfunction of ischaemic myocardium. Br J Pharmacol. 153 (6):1128-1132.

Wang GK, Calderon J, Wang SY. (2008) State- and use–dependent block of muscle Nav1.4 and neuronal Nav1.7 voltage–gated Na+ channel isoforms by ranolazine. Mol Pharmacol. 73 (3):940-948.

2. Rajamani S, Shroyck JC, Belardinelli L. (2008) Block of tetrodotoxin- sensitive, Na (V) 1.7 and tetrodotoxin-resistant, Na (V) 1.8, Na+ channels by ranolazine. Channels (Austin). 2(6):449-460.

3. Hunt S, Abraham W, Chin M, et al. (2007) ACC/AHA guidelines up–date for the diagnosis and management of chronic heart failure in the adult: summary article. Circulation. 115: 1825-1852.

4. Aysin B, Colombo J, Aysin E. (2007) Comparison of HRV analysis meth–ods during orthostatic challenge: HRV with respiration or with– out? 29th Int Conf IEEE EMBS Lyon, France.

5. Aksebrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen R.J. (1981) Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science. 213(4504):220-222.

6. Aksebrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen R.J. (1985) Hemodynamic regulation: investigation by spectral analysis. Am J Physiol. 249 (4 Pt 2):H867-H875.

7. Aksebrod S, Eliash S, Oz O, Cohen S. (1987) Hemodynamic regulation in SHR: investigation by spectral analysis. Am J Physiol. 253 (1 Pt 2):H176-H183.

8. Aksebrod S. (1988) Spectral analysis of fluctuations in cardiovascular parameters: a quantitative tool for the investigation of auto–nomic control. Trends Pharmacol Sci. 9(1):6-9.

9. Vinik AI, Ziegler D. (2007) Diabetic cardiovascular autonomic neuropa–thy. Circulation. 115(3):387-397.

10. Tomasselli GF, Zipes DP. (2004) What causes sudden death in heart failure? Circ Res. 95(8):754-763.

11. Maser RE, Mitchell BD, Vinik AI, Freeman R. (2003) The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. Diabetes Care. 26(6):1895-1901.

12. Watanabe J, Shinozaki T, Shiba N, et al. (2006) Accumulation of risk markers predicts the incidence of sudden death in patients with chronic heart failure. Eur J Heart Fail. 8(3):237-242.

13. Curtis BM, O’Keefe JH Jr. (2002) Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. Mayo Clin Proc. 77(1):45-54.

14. Umetani K, Ginter DH, McCrory R, Atkinson M. (1998) Twenty–four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. J Am Coll Cardiol. 31(3):593-601.

15. Frankenstein L, Zugck C, Schellberg D, et al. (2009) Prevalence and prognostic significance of adrenergic escape during chronic be–ta-blocker therapy in chronic heart failure. Eur J Heart Fail. 11(2):178-184.

16. Stein PK, Tereshchenko L, Domitrovich PP, Kleiger RE, Perez A, Deedwania P. (2007) Diastolic dysfunction and autonomic abnor–malties in patients with systolic heart failure. Eur J Heart Fail. 9(4):364-369.
18. Poirier P, Bogaty P, Philippon F, Garneau C, Fortin C, Dumesnil JG. (2003) Preclinical diabetic cardiomyopathy: relation of left ventricular diastolic dysfunction to cardiac autonomic neuropathy in men with uncomplicated well-controlled type 2 diabetes. Metabolism. 52(8):1056-1061.

19. Livanius EG, Flevari P, Theodorakis GN, Kolokathis F, Leftheriotis D, Kremastinos DT. (2003) Effect of biventricular pacing on heart rate variability in patients with chronic heart failure. Eur J Heart Fail. 5(2):175-178.

20. Stevens MJ, Raffel DM, Allman KC, Schwaiger M, Wieland DM. (1999) Regression and progression of cardiac sympathetic dysinnervation complicating diabetes: an assessment by C-11 hydroxyephedrine and positron emission tomography. Metabolism. 48(1):92-101.

21. Ziegler D, Gries FA. (1997) Alpha-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy. Diabetes. 46(Suppl 2):S62-S66.

22. Chaitman BR. (2006) Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. Circulation. 113(20):2462-2472.

23. Chaitman BR, Pepine CJ, Parker JO, et al. (2004) Combination Assessment of Ranolazine In Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial.

24. Chaitman BR, Skettino SL, Parker JO, et al. (2004) MARISA Investigators. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol. 43(8):1375-1382.

25. Ewing DI. (1978) Cardiovascular reflexes and autonomic neuropathy. Clin Sci Mol Med. 55(4):321-327.

26. Aysin B, Aysin E. (2006) Effect of respiration in heart rate variability (HRV) analysis. 28th Annual International Conference of IEEE Engineering in Medicine and Biology Society, New York, NY, Sep.

27. Malik M; (1996) Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation. 93(5):1043-1065.

28. Arora R, Ghosh Dastidar S, Colombo J. (2008) Age matched attenuation of autonomic activity in both branches in chronic hypertension. Clin Auton Res. 18(5):276.

29. Arora R, Ghosh Dastidar S, Colombo J. (2008) Altered sympathetic and parasympathetic activity is associated in patients with chronic coronary disease. Clin Auton Res. 18(5):276.

30. Arora R, Iffrig K, Colombo J. (2006) Chronic disease accelerates decline of autonomic responsivity. Clin Auton Res. 16:338.