Ranolazine Therapy Reduces Non-ST-Segment-Elevation Myocardial Infarction and Unstable Angina in Coronary Disease Patients with Angina

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Abstract

High sympathetic tone and cardiac autonomic neuropathy (CAN) are associated with major adverse cardiac events (MACE). We have shown ranolazine (RAN) improves autonomic function. RAN was introduced to 51 successive anginal CD patients (RANCD). A control group of 54 successive nonanginal CD patients (NORANCD) continued baseline therapy. Mean study duration was 6.1 years, which included semi-annual autonomic function measures (ANX 3.0, ANSAR Medical Technologies, Inc., Philadelphia, PA) and yearly myocardial perfusion SPECT studies (MPI). MACE were experienced by 29% RANCD patients versus 46% NORANCD patients ($p = 0.0105$). The patients from both groups with abnormal parasympathetic and sympathetic (P&S) measures and MACE totaled 52 of those patients with MACE versus 17% of those patients without MACE ($p = 0.0274$). Abnormal MPI was demonstrated in 35% of those with abnormal (P&S) measures and MACE versus 12% without MACE. Sympathovagal balance (SB) was lower, indicating higher, relative parasympathetic tone (known to be cardioprotective) in the RANCD group. Acute coronary syndromes occurred 4.5 times as often in NORANCD patients. High SB occur more frequently than abnormal MPI in CD patients experiencing MACE. In addition to increased myocardial blood flow as its proposed mechanism of angina relief, RAN improves P&S measures, a potentially new mechanism whereby RAN improves outcomes.

Keywords
- ranolazine
- coronary disease
- acute coronary syndrome
- cardiac autonomic neuropathy
- parasympathetic function
- sympathetic function
- major adverse cardiac events

High sympathetic tone and cardiac autonomic neuropathy (CAN; defined as very low parasympathetic activity) have been associated with acute coronary events, congestive heart failure (CHF), malignant ventricular arrhythmias, and increased mortality.[1–8] High sympathetic tone is predictive of future coronary events,[9] and good parasympathetic tone is protective.[10] We discovered that ranolazine (RAN) reduces high sympathetic tone and increases parasympathetic tone in CHF, thereby improving sympathovagal balance (SB), most likely by inhibiting neuronal sodium channel 1.7 ($Na_v1.7$).[11] Therefore, we postulated that RAN might reduce acute coronary events and deaths in patients with coronary disease (CD). This article documents changes in parasympathetic and sympathetic (P&S) measures in CHF patients treated with RAN added to guideline-driven therapy.

Methods

Beginning in 2006, 51 successive previously revascularized CD patients with angina were treated with RAN, 500 to 1,000 mg twice daily orally, added to their pharmacologic therapy. The patients were followed while recording the occurrence of major adverse cardiac events (MACE). We define MACE as: (1) acute coronary syndromes (ACS), including unstable angina, ST-segment elevation, and non-ST-segment elevation myocardial infarction (STEMI and NSTEMI, respectively); (2) elective revascularization; or (3) cardiac death (per death certificate). Outcomes in RAN-treated patients (RANCD) were compared with a cohort of 54 successive revascularized CD patients (NORANCD) without

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angina who were not given RAN. P&S function was assessed noninvasively using the ANX-3.0 autonomic monitor (ANSAR Medical Technologies, Inc., Philadelphia, PA). P&S activity was computed simultaneously and independently based on concurrent, continuous, time-frequency analyses of respiratory activity (RA) and heart rate variability (HRV).[12–16] Parasympathetic activity (measured as the respiratory frequency area [RFa]) is defined as the spectral power within a 0.12-Hz-wide window centered on the fundamental respiratory frequency (FRF) in the HRV spectrum. FRF is identified as the peak spectral mode from time-frequency analysis of RA. Effectively, FRF is a measure of vagal outflow as it affects the heart (a measure of cardiovagal activity). Sympathetic activity (low-frequency area [LFa]) is defined as the remaining spectral power, after computation of RFa, in the low-frequency window (0.04–0.15 Hz) of the HRV spectrum. High SB is defined as a resting LFa/RFa ratio >3.0 (established in our laboratory by evaluating 260 healthy volunteers).[11]

P&S activity was recorded from a standard autonomic test, including: 5-minute rest, 1-minute paced breathing (6 breaths/minute), a Valsalva challenge (including a 15-second Valsalva maneuver), and a quick stand followed by 5 minutes of quiet stand. The average SB reported is the average of the ratios recorded during the sampling period, not a ratio of averages.[11] The 30:15 ratio is the ratio of the 30th heart beat interval (HBI) after a quick head-up postural change (standing) to the 15th HBI after standing. The 30:15 ratio reflects the reflex bradycardia upon standing that depends on sympathetic vasoconstriction.[17] The Valsalva ratio is the ratio of the longest HBI to the shortest HBI during a 15-second Valsalva maneuver.[17] The E/I ratio is the ratio of the HBI during peak exhalation over that during peak inhalation during paced breathing. All three (time-domain) ratios are relative measures of more, or less, Vagal tone. CAN was defined in standard fashion,[1] reflecting very low parasympathetic activity. P&S measures were taken every 6 months.

Yearly single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI) studies were done. Antianginal medications were administered 24 hours prior to MPI. For exercise SPECT MPI, 10 MCi technetium (Tc)-99m Tetrofosmin were given intravenously (IV) at rest. Thereafter, SPECT images were acquired within 20 to 40 minutes, under a double-headed gamma camera with high-resolution collimation. At peak exercise (all patients achieved target heart rate) 30 MCi of Tc-99m Tetrofosmin were injected IV, stress images acquired 20 to 40 minutes later in a 64 × 64 matrix, with 64 projections, 20-second stops, and 8 frames per cycle with a 20% window centered on the 140-KeV photopeak of Tc-99m. The stress study was gated to evaluate regional wall motion and to calculate left ventricular ejection fraction. Resting images were acquired in the same 64 × 64 matrix with 64 projections and 20-second stops. Data were reconstructed in the short, horizontal long, and vertical long axis views, and tomographic slices were generated. For pharmacologic stress, 0.4-mg regadenoson were given IV, and 1 minute later 30 mCi Tc-99m Tetrofosmin were injected. Gating was performed 60 minutes thereafter. Polar maps were divided into 20 segments. Patients signed appropriate consent forms for all performed procedures.

Statistics

Fisher exact test of statistical significance was used to analyze the independence of the relatively small sample sizes in the 2 × 2 contingency tables derived from the study.

Results

The patient demographics are presented in ►**Table 1**. RANCD patients had a higher past history of CHF (12 of 51, 24%) than NORANCD patients (4 of 54, 7%); otherwise, the two populations were similar in all respects. A total of 15 of 51 (29%) RANCD patients suffered MACE versus 25 of 54 (46%) NORANCD patients ($p < 0.0105$; ►**Table 2**). ACS occurred 2.77 times as frequently in NORANCD patients: 9 of 25 events (36%) in NORANCD versus 2 of 15 events (13%) in RANCD patients. Cardiac death happened in 3 of 15 (20%) of RANCD event patients versus 3 of 25 (12%) of NORANCD event patients. Revascularization rates were similar in RANCD and NORANCD event patients: 10 of 15 (66.7%) versus 13 of 25 (52%), respectively. ►**Table 1** lists the following differences in subjects with versus without events: patients who experienced MACE more often had reversible defects on stress tests and a history of multivessel CD. Ischemic stress tests (+MPI) resulted in 14 of 40 event patients (35%) versus 8 of 65 nonevent patients (12%). Multivessel CD was demonstrated in 30 of 40 event patients (75%) versus 35 of 65 nonevent patients (54%).

The noninvasive autonomic (P&S) measures are shown in ►**Tables 3** and **4**. The final P&S results were the last taken before an event or the last recorded follow-up in patients without events. RANCD patients had lower SB (1.99, vs. 2.34 in NORANCD patients; $p = 0.0346$), higher RFa (0.85 vs. 0.73 bpm^2 in NORANCD patients; $p = 0.0262$), and a lower incidence of high SB or CAN (13 of 51 patients [25.5%] vs. 19 of 54 NORANCD patients [35.2%]; $p = 0.0439$; ►**Table 3**). Patients with events more often had high SB than patients without events (17 of 40 patients [42.5%] vs. 7 of 65 patients [10.8%], respectively; $p = 0.0237$; ►**Table 3**). When comparing P&S measures in RANCD versus NORANCD patients with and without events (►**Table 4**), one significant difference (i.e., $p < 0.05$) was found: 9 of 36 (36%) RANCD patients without events initially had high SB that persisted in only 3 patients (8.3%) following RAN therapy; in comparison, 7 of 29 (24%) of NORANCD patients who did not have an event initially had high SB that remained throughout follow-up in 4 patients (13.8%; $p = 0.0275$ for the change in high SB).

Discussion

The principal finding of this study is that RANCD patients experienced 37% fewer MACE than NORANCD patients, 15 of 51 (29%) versus 25 of 54 (46%), respectively, the difference mainly being due to a 64% reduction in ACS (►**Table 2**). The RANCD and NORANCD groups were similar in all respects, except that the RANCD population had more subjects with a past history of CHF, 12 of 51 (24%) versus 4 of 54 (7%), as shown in ►**Table 1**. Patients with MACE were more likely to have multivessel disease (30 of 40 [75%] patients vs. 35 of 65 [54%] patients without MACE) and +MPI (14 of 40 [35%] patients vs. 8 of 65 [12%] patients without MACE; ►**Table 1**). Previously

Table 1 Patient demographics

	RANCD ($N = 51$)	NORANCD ($N = 54$)	EVENT ($N = 40$)	NO EVENT ($N = 65$)
Age (mean)	64 y	65 y	65 y	64 y
Gender	M: 40/51 (78%); F: 11/51 (22%)	M: 38/54 (70%); F: 16/54 (30%)	M: 31/40 (78%); F: 9/40 (22%)	M: 47/65 (72%); F: 18/65 (28%)
Revascularization				
CABG	27/51 (53%)	25/54 (46%)	22/40 (55%)	31/65 (48%)
Stent	24/51 (47%)	29/54 (54%)	18/40 (45%)	34/65 (52%)
PHx				
MI	19/51 (37%)	24/54 (44%)	17/40 (35%)	27/65 (42%)
CHF	12/51 (24%)	4/54 (7%)	6/40 (15%)	8/65 (12%)
DM	30/51 (59%)	28/54 (52%)	19/40 (48%)	38/65 (58%)
HTN	38/51 (75%)	38/54 (70%)	27/40 (68%)	49/65 (75%)
HL	47/51 (92%)	50/54 (93%)	36/40 (90%)	63/65 (97%)
PAD	6/51 (12%)	7/54 (13%)	7/40 (17.5%)	6/65 (9%)
CRD	3/51 (6%)	4/54 (7%)	4/40 (10%)	3/65 (5%)
Smoking (active)	9/51 (18%)	9/54 (17%)	6/40 (15%)	10/65 (15%)
Beta blocker	30/51 (59%)	30/54 (56%)	18/40 (45%)	37/65 (57%)
Carvedilol	35 mg/d	31 mg/d	33 mg/d	33 mg/d
Metoprolol	79 mg/d	73 mg/d	70 mg/d	70 mg/d
ASA	51/51(100%)	54/54 (100%)	40/40 (100%)	65/65 (100%)
Statin	38/51 (75%)	40/54 (70%)	33/40 (83%)	47/65 (72%)
ACE-I/ARB	35/51 (69%)	38/54 (70%)	33/40 (83%)	40/65 (62%)
CC blocker	13/51 (25%)	14/54 (26%)	11/40 (28%)	16/65 (25%)
+ MPI	10/51 (20%)	12/54 (22%)	14/40(35%)	8/65 (12%)
Cardiac catheterization				
1V NLAD	9/51 (17.6%)	15/54 (27.8%)	6/40 (15%)	18/65 (27.7%)
1V LAD	10/51 (19.6%)	6/54 (11.1%)	4/40 (10%)	12/65 (18.5%)
2V NLAD	2/51 (3.9%)	1/54 (1.9%)	2/40 (5%)	1/65 (1.5%)
2V LAD	11/51 (21.6%)	15/54 (27.8%)	12/40 (30%)	14/65 (21.5%)
3V	19/51 (37.25%)	17/54 (31.5%)	16/40 (40%)	20/65 (31%)
LVEF	0.56	0.60	0.55	0.59
Follow-up (mean)	6.19 y	5.94 y	6.19 y	5.94 y

Abbreviations: +, positive for ischemia; ACE/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ASA, aspirin; CABG, coronary artery bypass surgery; CC, calcium channel; CHF, congestive heart failure; CRD, chronic renal disease; DM, diabetes mellitus; F, female; HL, hyperlipidemia; HTN, hypertension; LAD, left anterior descending; LVEF, left ventricular ejection fraction; M, male; MI, myocardial infarction; MPI, myocardial perfusion imaging; NLAD, non-LAD; PAD, peripheral arterial disease; V, vessel.

revascularized CD patients were chosen for this study because it was felt that their event rates would be higher than CD subjects without a past history of revascularization.

RAN blocks neuronal Na_v 1.7 in a strongly use-dependent fashion via the local anesthetic receptor.[18,19] We proposed this as the mechanism whereby RAN directly reduces high SB and improves RFa in CHF patients.[11] Since high sympathetic tone is predictive of, and associated with, acute coronary events,[5–9] and parasympathetic tone is protective,[10] it was felt that RAN might offer unique benefits in CD patients. Indeed, RANCD patients demonstrated lower SB and higher RFa than NORANCD patients (►**Table 3**). CD patients who suffered MACE had higher SB and lower RFa, including more CAN (primarily reflecting very low parasympathetic tone) than subjects without MACE (►**Tables 3** and **4**). Importantly, 9 of 36 (36%) RANCD patients without MACE during follow-up initially had high SB prior to RAN therapy; in only 3 of these 36 (8.3%) did this high SB persist after RAN. Since 17 of 24 (71%) patients with persistently high SB had MACE (►**Table 3**), had the high SB in these 9 RANCD patients continued, another 6 patients should have experienced MACE. This would have resulted in 21 of 51 (41%) RANCD

Table 2 Major adverse cardiac events (MACE)

	RANCD	NORANCD
Total events	15/51 (29%)	25/54 (46%)
Revascularization		
Stent	8/15 (53%)	13/25 (52%)
CABG	2/15 (13%)	0
ACS		
NSTEMI	2/15 (13%)	6/25 (24%)
UA	0	3/25 (12%)
Death	3/15 (20%)	3/25 (12%)

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; NORANCD, coronary disease patients not treated with ranolazine; NSTEMI, non-ST-segment elevation myocardial infarction; RANCD, coronary disease patients treated with ranolazine; UA, unstable angina.

Table 3 Final P&S measures (mean values)

	RANCD ($N = 51$)	NORANCD ($N = 54$)	*p*-Value	Event ($N = 40$)	No event ($N = 65$)	*p*-Value
SB	1.99	2.34	0.0346	2.91	1.73	0.0105
RFa	0.85	0.73	0.0262	0.64	0.88	0.0268
E/I	1.11	1.09	0.1370	1.12	1.08	0.0102
VR	1.22	1.09	0.0414	1.20	1.18	0.1516
30:15	1.16	1.12	0.5520	1.11	1.16	0.0635
Hi SB	10/51 (19.6%)	14/54 (25.9%)	0.0439	17/40 (42.5%)	7/65 (10.8%)	0.0237
CAN	3/51 (5.9%)	5/54 (9.3%)	0.0791	4/40 (10%)	4/65 (6.2%)	0.0245

Abbreviations: CAN, cardiac autonomic neuropathy; E/I, exhalation to inhalation ratio (unitless); NORANCD, coronary disease patients not treated with ranolazine; RANCD, coronary disease patients treated with ranolazine; RFa, respiratory frequency area in beats per minute squared (bpm^2); SB, sympathovagal balance; VR, Valsalva ratio (unitless); 30:15, 30 to 15 ratio (unitless).

Table 4 Final P&S measures in event versus no event patients (mean values)

	Event patients			No event patients		
	RANCD ($N = 15$)	NORANCD ($N = 25$)	*p*-Value	RANCD ($N = 36$)	NORANCD ($N = 29$)	*p*-Value
SB	2.83	2.95	0.0699	1.65	1.82	0.0641
RFa	0.80	0.55	0.0358	0.87	0.89	0.0829
E/I	1.19	1.08	0.4837	1.07	1.09	0.4111
VR	1.34	1.12	0.0764	1.17	1.20	0.4105
30:15	1.13	1.10	0.4601	1.18	1.14	0.0681
Hi SB	7/15 (46.7%)	10/25 (40%)	0.1605	3/36 (8.3%)[a]	4/29 (13.8%)	0.0275
CAN	1/15 (6.7%)	3/25 (12%)	0.0123	2/36 (5.6%)	2/29 (6.9%)	0.2653

Abbreviations: CAN, cardiac autonomic neuropathy; E/I, exhalation to inhalation ratio (unitless); NORANCD, coronary disease patients not treated with ranolazine; RANCD, coronary disease patients treated with ranolazine; RFa, respiratory frequency area in beats per minute squared (bpm^2); SB, sympathovagal balance; VR, Valsalva ratio (unitless); 30:15, 30 to 15 ratio (unitless).
[a]Initially, 9/36 (36%) RANCD patients had high SB versus 7/29 (24%) NORANCD patients.

patients with MACE, comparable to the 25 of 54 (46%) incidence of MACE in the NORANCD group.

High SB was used as a measure of (relative) sympathetic excess, rather than LFa, because absolute LFa (and RFa) decreases with age and some chronic conditions.[20–22] The normal range for SB of 0.4 to 3.0 (unitless) was established in our laboratory by studying 260 subjects with no obvious reason for autonomic dysfunction. This range matches that of the manufacturer. 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 (FFT). Although FFT, including short-term FFTs, is accurate for

stationary signals, it causes a compromise between time and frequency resolution due to fixed length windows used in analysis. The P&S activity monitored during clinical testing, including the Ewing challenges, 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.[16] Second, instead of assuming that parasympathetic modulation always lies within the 0.15 to 0.40 Hz frequency range, P&S monitoring measures parasympathetic modulation from a second independent measure of the autonomic nervous system: RA (e.g., via impedance plethysmography). Since respiratory sinus arrhythmia is purely parasympathetic in etiology,[12–16] spectral analysis of RA is a measure of vagal input to the heart. This measure has been labeled the FRF.[12] For example, if a patient's respiratory rate (FRF) is very slow, parasympathetic activity would, at least in part, be contained within the low-frequency range of HRV. 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.[17] 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 6 breaths per minute, or 0.10 Hz. This causes a significant increase in the low-frequency HRV with little or no change in high-frequency HRV measures.[16] 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.[17] 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.[16]

CAN has been associated with silent myocardial infarction, increased mortality, CHF, and malignant ventricular arrhythmias.[1] CAN is most commonly, but not exclusively, found in diabetics. It indicates critically low RFa regardless of LFa (LFa risk stratifies RFa[23]). Only 8 patients had CAN: 4 of 40 (10%) patients suffering MACE and 4 of 65 (6.2%) patients without MACE, $p = 0.0245$—3 of 51 (5.8%) RANCD patients and 5 of 54 (9.2%) NORANCD patients, $p = 0.0791$ (►**Table 3**). Obviously, too few patients had CAN to permit meaningful comparisons. However, RFa was higher in RANCD patients than NORANCD patients, 0.85 versus 0.73 bpm^2 ($p = 0.0262$; ►**Table 3**), as well as in patients without events than in event patients, 0.88 bpm^2 versus 0.64 bpm^2 ($p = 0.0268$; ►**Table 3**), respectively. These findings are consistent with RAN increasing parasympathetic tone and its protective effect.

Why RAN failed to decrease SB in RANCD event patients to the SB level of RANCD patients without events (►**Table 4**) cannot be determined with certainty. RAN dosing in these patients was the same. More event patients had multivessel CD than patients without events (►**Table 1**), and multivessel CD has been associated with increased sympathetic activity.[24]

Limitations

This is an open-label single-center study involving 105 patients. Patients were not randomized to RAN or NORAN therapy, although the two therapeutic groups were quite similar (►**Table 1**), because patients given RAN had angina, the FDA indication for the drug, and patients not given RAN were free of angina at entry. The strength of the study is the length of time patients were followed.

Conclusion

RAN reduces MACE in CD patients, especially ACS. Abnormal P&S measures, especially higher SB and lower RFa, occur more frequently than reversible defects on MPI in CD patients experiencing MACE. In addition to improving myocardial blood flow as its proposed mechanism of angina relief, RAN improves P&S measures, a new mechanism of action whereby RAN improves outcomes.

Disclosures

Dr. Colombo is a part owner, employee, Medical Director, and Executive VP of ANSAR Medical Technologies, Inc.

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