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Review Article

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Increased Sympathetic Tone in Congestive Heart Failure and Comorbid Pain-Acute Friend Turns Chronic Foe and a Novel Pharmacologic Corrective Approach

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Abstract

Acute pain and congestive heart failure (CHF) both increase sympathetic (S) tone, decreasing pain and improving cardiac output. However, chronically high S increases pain and worsens CHF. Mechanisms will be discussed, and off-label ranolazine is a novel potential pharmacologic remedy in chronic CHF: (1) Fifty-four CHF patients were randomized to adjunctive RAN (RANCHF, 1000mg bid) vs. NORANCHF. Autonomic measurements (ANX 3.0 Autonomic Monitor) were taken at baseline and 1 yr. Fifty-nine % of patients in both groups were initially abnormal, including high sympathovagal balance (SB) that normalized in 10/12 (83%) RANCHF patients vs. 2/11 (18%) NORANCHF patients. High SB developed in 5/11 (45%) NORANCHF vs. 1/11(9%) RANCHF patients; (2) Matched CHF patients were given adjunctive RAN (1000 mg po-bid) (RANCHF, 41 systolic, 13 diastolic) vs. 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/fibrillation[vt/vf] by 40 % In conclusion, RAN substantially corrects the maladaptive SNS CHF response. Since 1 mechanism of action of RAN is a strongly use-dependent inhibition of the Nav1.7 in S ganglia, RAN should provide pain relief in chronically S-mediated pain syndromes.

Keywords: Complex Regional Pain Syndrome, Ranolazine, Sympathetic-Mediated Pain

Introduction

CHF and many chronic pain syndromes, such as complex regional pain (CRPS), share high S tone which, while helpful acutely, is extremely harmful chronically. 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 2 studies. We propose RAN should benefit chronically S-mediated pain as well, since much of the pathophysiology is shared in both conditions.

Activation of the SNS 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 [1]. As a result, SNS output increases, and plasma levels of norepinephrine NE can be 2-3 times normal, increasing α2 activity and afterload, left ventricular hypertrophy (LVH), and are predictive of mortality [2, 3]. NE stimulates the cardiac β1 receptor (β1 -AR), activating the Protein Kinase A pathway [3, 4]. These changes are the same whether the CHF is systolic (HFrEF) or diastolic (HFpEF).

The Catecholamine Pka Pathway

Catecholamines bind to the transmembrane G-coupled β_1 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) increasing systolic C^{a++} entry, and bind PKA to the sarcoplasmic reticulum to enhance the activities of ryanodine receptors (Ry Rs [Ca++ - mediated Ca^{++} release, a + inotropic effect]) and sarco-

endoplasmic reticulum Ca^{++} - ATPase (SERCA [Ca^{++} reuptake, a $^{+}$ lusitropic effect) [3]. PKA also phosphorylates Phospholamban (PLN) increasing SERCA activity and contributing to + chronotropy [4, 5]. PKA phosphorylation of cardiac myosin-binding protein C (cMyBP-C) weakens inhibition of myosin, increasing force-producing myosin heads and accelerating cross-bridge cycling (+inotropy and + lusitropy) [6-9].

The Catecholamine PKA Pathway in CHF

Chronically stimulated β_1 ARs are downregulated by β-arrestin-mediated internalization and desensitized by uncoupling from G-proteins, reducing the SNS's ability to increase LV contractility (+ inotropy) and improve diastolic dysfunction and Titin compliance (+lusitropy) via catecholamine activation of PKA, thereby worsening CHF [3,10]. Chronic LTCC activation, resulting in Ca++ overload, causes myocardial necrosis (increased intracellular Ca++ from any cause results in activation of the mitochondrial death pathway) [3]. Constitutive PKA activation hyperphosphorylates RyR2(diastolic Ca^{++} leak depleting SR Ca^{++} and causing diastolic contractions) and PLN, increasing intracellular Ca^{++}, reducing inotropy/lusitropy, and can even eventuate in a dilated cardiomyopathy and sudden death[11].

PKA's interaction with its anchoring proteins is reduced in CHF, and anchoring proteins are down-regulated [12, 13].

CHF also alters phosphodiesterase (PDE), the enzyme converting c-ATP to AMP, isoforms. Decreased PDE3A and PDE4D trigger a SR C a^{++}leak, contributing to cytosolic Ca^{++} overload and arrhythmia-provoking afterpotentials, and apoptosis; increased PDE1C, PDE2, and PDE10A reduce cAMP and contractility (-inotropy). Increased β, AR activity also reduces PKA signaling [3, 14-18].

Expressed simply, acute PKA stimulation improves CHF, while chronic stimulation worsens it.

Sympathetic Ganglia Neuronal Sodium Channel 1.7 (Nav1.7) and Ranolazine (Ran)

Nav1.7 is blocked in its open state in a strongly use-dependent manner by RAN via the local anesthetic receptor [19, 20]. Therefore, RAN's reduction of SNS β1 AR stimulation should increase as SNS tone increases. We administered RAN 1000mg p.o. b.i.d. to 30 subjects without CHF or an indication for RAN who had "CHF-like" high SB (>2.5) [Table 1] [21]. On the 5th 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 P&S responses in 30 patients without CHF or angina

Rest	preRAN SD	Post-RAN SD	p
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).

Ranolazine and CHF

Fifty-four demographically matched, Guideline-treated CHF patients were randomized to (1) open-label RAN (RANCHF) added to usual therapy vs. (2) usual therapy (NORANCHF) [21]. Parasympathetic and sympathetic (P&S) measurements were taken at baseline and at 12 months. Baseline ANS measures were abnormal in 59% of patients in each group [Table 2].

Table 2: Changes in abnormal P&S measures in RANCHF vs. NORANCHF patients without arrhythmia

P&S (M ± SD)	RANCHF(n = 16)			NORANCHF(n = 16)		
Rest	preRAN	12 months	p	Initial	12 months	p
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
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).

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 415 patient study [22]. 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 2nd study to evaluate RAN's effect upon LVEF, Matched CHF patients 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) [Table 4] [23]. 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. 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 3].

Table 3: Baseline and follow-up P&S measures and LVEF from age-, gender- and history-matched, arrhythmia-free patients: RANCHF vs.NORANCHF

Rest	RANCHF (N = 46)			NORANCHF (N = 49)		
	Initial	Final	p	Initial	Final	p
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	0.267
E/I ratio	1.11	1.09	0.552	1.11	1.11	0.156
Valsalva challenge						
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).

RAN reduced MACE by 40%: sudden death 5.6% vs. 12.77%; VT/VF 11.1% vs. 25.6%; CHF admission 22.2% vs. 27.3%.

Although improvements in LVEF and outcomes correlated with reduction of SNS tone, RAN has a 2nd , independent method of action that improves LVEF and outcomes. By binding to amino acid F1760 of the cardiac sodium channel 1.5(Nav1.5), 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 [23].

The S nervous system and pain (24)

Acute pain increases S tone, while chronically high S can increase chronic pain. Dendritic cells activated by inflammation downregulate β2 receptors that reduce cell migration, and upregulate α1 receptor-mediated cellular migration, releasing proinflammatory cytokines, and activating nociceptors, as does NE released by efferent Ss.

Inflammatory conditions have a neurogenic activation of C-fibers, releasing vasodilatory neuropeptides, e.g. neurogenic inflammation.

Patients are likely to become anxious. Treating the autonomic nervous system abnormalities significantly relieves this [24, 25].

Conclusions

The autonomic changes resulting from chronic CHF and chronic pain syndromes are analogous. Since off-label RAN has such a remarkable ability to reduce S-tone and major adverse cardiac events by 25-55%, it is felt that sympathetically-mediated chronic pain should respond as well.

References

1. Floras J (2003) Sympathetic activation in human heart failure: Disease mechanisms, therapeutic opportunities. Acta Physio Scand. 177: 391.
2. Lutz Frankenstein, Christian Zugck, Dieter Schellberg, Manfred Nelles and Hanna Froehlich, et al. (2009). Prevalence and prognostic significance of adrenergic escape during chronic beta-blocker therapy in chronic heart failure. Eur J Heart Fail.11:178-184.
3. Liu Y, Chen J, Fontes S, Bautista E and Cheng Z (2021). Physiological and pathological roles of protein kinase A in the heart. Cardiovascular Research. 00: 1-13.
4. Vinogradova T, Lyashkov A, Zhu W, Ruknudin A and Sirenko S, et al. (2006). High protein kinase A- dependent phosphorylation drives rhythmic internal Ca2+ store oscillations and spontaneous beating of cardiac pacemaker cells. Circ Res. 98: 505-514.
5. Kranais E and Haijar R (2012) Modulation of cardiac contractility by the phospholamban/SERCA2a regulatome. Circ Res. 110: 1646-1660.
6. McNamara J, Singh R, Sadayappan S (2019). Cardiac myosin binding protein-C phosphorylation regulates the super-relaxed state of myosin. Proc Natl Acad Sci USA. 116: 11731-11736.
7. Mamid R, Gresham K, Stelzer J (2017). Cardiac myosin binding protein-C Ser (302) phosphorylation regulates cardiac beta-adrenergic reserve. Sci Adv. 3: e1602445.
8. Rosas P, Liu Y, Abdalla M, Thomas C and Kidwell D, et. al. (2015). Phosphorylation of cardiac myosin-binding protein-C is a critical mediator of diastolic function. Circ Heart Fail. 8: 582-594.
9. Gresham K and Stelzer J (2016). The contributions of cardiac myosin binding protein C and troponin I phosphorylation to beta-adrenergic enhancement of in vivo cardiac function. J Physiol. 594: 669-686.
10. Wang J, Gareri C, Rockman H (2018). G-protein-coupled receptors in heart disease. Circ Res. 123: 716-735.
11. Antos C, Frey N, Marx S, Reiken S and Gaburjakova M, et, al. (2001). Dilated cardiomyopathy and sudden death resulting from constitutive activation of protein kinase A. Circ Res. 89: 997-1004.
12. Aye T, Soni S, van Veen T, van der Heyden M and Cappadona S, et al. (2012) Reorganized PKA-AKAP associations in the failing human heart. J Mol Cell Cardiol. 52: 511-518.
13. Li L, Li J, Drum B, Chen Y and Yin H, et al. (2017). Loss of AKAP150 promotes pathological remodeling and heart failure propensity by disrupting calcium cycling and contractile reserve. Cardiovasc Res. 113:147-159.
14. Lehnart S, Wehrens N, Reiken S, Warner S and Belevych A, et al. (2005). Phosphodiesterase 4D deficiency in the ryanodine receptor complex promotes heart failure and arrhythmias. Cell. 123: 25-35.
15. Poldovitch N, Yang S, Sun H, Lakin R and Ahmad F, et al. (2019). Phosphodiesterase type 3A (pde3a) but not type 3B (PDE3B) contributes to the adverse cardiac remodeling induced by pressure overload. J Mol Cell Cardiol. 132: 60-70.
16. Knight W, Chen S, Zhang Y, Oikawa M and Wu M, et al. (2016). PDE1C deficiency antagonizes pathological cardiac remodeling and dysfunction. Proc Natl Acad Sci USA. 113: E7116-E7125.
17. Chen S, Zhang Y, Lighthouse J, Mckelsen D and Wu J, et al. (2020). A novel role of cyclic nucleotide phosphodiesterase 10A in pathological cardiac remodeling and dysfunction. Circulation. 141: 217-233.
18. Mehel H, Emons J, Vettel C, Wittkopper K and Seppelt D, et al. (2013) Phosphodiesterase-2 is up-regulated in human failing hearts and blunts beta-adrenergic responses in cardiomyocytes. J Am Coll Cardiol. 62: 1596-1606.
19. Wang GK, Calderon J and 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. 73:940-948.
20. Rajamani S, Shryock JC and 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: 449-460.
21. Murray G and Colombo J (2014). Ranolazine improves autonomic balance in heart failure when added to guideline-driven therapy. Heart International. 9: 59-65.
22. L Frankenstein, Christian Z, D Schellberg, M Nelles and H Froehlich, et al. (2009). Prevalence and prognostic significance of adrenergic escape during chronic beta-blocker therapy in chronic heart failure. Eur J Heart Fail. 11: 178-184.
23. Murray G and Colombo J (2014). Ranolazine preserves and improves left ventricular ejection fraction and autonomic measures when added to guideline-driven therapy in chronic heart failure. Heart International. 9: 66-73.
24. Schlereth T and Birklein F (2008). The sympathetic nervous system and pain.Neuromol Med. 10:141-147.
25. Colombo J, Murray GL, Pinales JM, Acosta C and Lill R, et al. (2020). Parasympathetic and Sympathetic Nervous Systems Measurements and Anxiety-Like Symptoms: Improved Differentiation and Improved Outcomes. Cardiol Open Access. 5:19-25.