

Prolonged, Untreated Autonomic Dysfunction May Ultimately Lead to Heart Failure

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ABSTRACT

Background. There is extensive evidence for a significant correlation between high Pulse Pressure (PP) and the occurrence of cardiovascular events, including Heart Failure (HF), both in normotensive and hypertensive subjects. HF is a known predictor of mortality risk in HF patients. PP is affected by the two Autonomic branches: the Parasympathetics and the Sympathetics (P&S). Autonomic dysfunction is strongly associated with abnormal PPs.

Objective. Here, we propose a possible P&S mechanism which is known to lead to abnormal BPs and, if prolonged, abnormal PPs: Sympathetic Withdrawal (SW), which leads to Orthostatic dysfunction, which may lead to poor coronary perfusion and decreased diastolic BP, which may lead to increased resting systolic BP, which often rises as a compensatory against poor coronary and cerebral perfusion, which leads to widening of PP, which may indicate HF. **Methods.** SW is measured with P&S Monitoring (Physio PS, Inc., Atlanta, GA), serially for 9445 patients (4731 female, 50.1%; average age 68.9 yrs, range 40 to 100 y/o; average BMI 28.9 #/in²). PP & HF are determined in the classical manner. **Results.** Patients' LVEFs are within normal limits. HF is the primary diagnoses in 35.2%. SW is prevalent, 56.1% (p<0.001). Within the SW sub-population, 24.5% have low diastolic BP (p=0.23), 53.4% have high systolic BP (p=0.041), 75.0% have wide PPs (p=0.001), and 18.6% demonstrate high risk of cardiovascular disease (p=0.014). **Conclusion.** Even in a seemingly well-managed cardiology cohort, 40.1% of the population are at risk for HF. SW may be treated, and often relieved, with oral vasopressors, which, if prescribed early, may prevent HF.

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INTRODUCTION

Heart Failure (HF) is a complex clinical syndrome [1]. Its prevalence makes it one of the top reasons for admission to the Emergency Department and one of the most expensive Diagnosis Related Groups. Peripheral Pulse Pressure (PP), the difference between systolic and diastolic blood pressures (BPs), is well known to be influenced primarily by left ventricular ejection fraction (LVEF) and aortic stiffness. PP markedly rises after the fifth decade of

life due to arterial stiffening with increasing age. There is extensive evidence for a significant correlation between high PP and the occurrence of cardiovascular (CV) events, including HF, both in normotensive and hypertensive subjects [2]. HF is a known predictor of mortality risk in HF patients [3]. PP is easily and reliably used in clinical practice as a prognostic marker [4]. BP, including PP, is affected by the two branches of the autonomic nervous system: the Parasympathetics and the Sympathetics

(P&S). Autonomic dysfunction is strongly associated with abnormal BPs.

Heretofore, independent, simultaneous measures of P&S activity have been difficult at best. Now, P&S measures are available both at rest and in response to challenges. P&S measures are available in an easy-to-use clinical application [5]. Autonomic (P&S) dysfunctions may lead to a cascade of events that lead to abnormal BPs, which in turn may lead to abnormal PPs, which may lead to HF. Serial testing with P&S Monitoring enables the tracking of the morbidity and mortality risks associated with HF. This enables earlier detection, permitting earlier intervention, helping to result in improved patient outcomes. One P&S dysfunction that is known to lead to abnormal BPs is Sympathetic Withdrawal (SW). SW is an abnormal decrease in alpha-Sympathetic activity upon assuming a head-up posture (sitting up or standing) [6].

HYPOTHESIS

Here, we propose a possible P&S mechanism which is known to lead to abnormal BPs and, if prolonged, abnormal PPs:

1. SW is known to lead to decreases in BP upon standing due to the pooling of blood in the lower extremities. If undetected, SW eventually leads to lightheadedness due to Orthostatic dysfunction (*e.g.*, Orthostatic Hypotension);
2. With prolonged SW, the pooling of blood leads to a reduction in diastolic BP and poor coronary perfusion;
3. With prolonged SW, resting systolic BP often rises apparently as a compensatory mechanism against the drop in BP upon standing, helping to prevent poor coronary and ultimately cerebral perfusion;
4. Often with SW, patients are unresponsive to anti-hypertensives due to the body's compensatory mechanism attempting to maintain proper cerebral perfusion, and as a result, further increases in systolic BP and further decreases in diastolic BP may occur, widening PP;
5. With these conditions, prolonged PP widens sufficiently to induce CV disease (CVD), including HF.

This mechanism may enable earlier detection of HF risk and earlier intervention to reduce or prevent HF.

METHODS

From two, suburban, cardiovascular and autonomic (P&S) dysfunction clinics in the mid-western and northeastern United States of America (USA), 9445 patients (4731 female, 50.1%; average age 68.9 yrs, range 40 to 100 y/o; average BMI 28.9 #/in²) previously diagnosed with CVD, including hypertension or autonomic dysfunction, were tested serially from January 2012 through July 2020. Detailed patient histories and physicals were taken as routine. Age-appropriate and symptom-specific cardiology testing, included EKGs, Stress tests, Echocardiograms, and indicated blood work, were ordered according to standards. Indicated autonomic testing, including tilt-table testing (TMFlow, Wake Forest, NC); Vestibular testing; Mast Cell blood work; Small Fiber Neuropathy testing; and serial P&S Monitoring (Physio PS, Atlanta, GA), which includes the Ewing challenges, were ordered as well.

P&S Monitoring includes LFa as the direct measure of Sympathetic (S) activity, RFa as the direct measure of Parasympathetic (P) activity, and Sympathovagal Balance ($SB=S/P$, measured at rest as the average of ratios, not the ratio of averages) [5]. P&S Monitoring entails collecting P&S activity from five minutes of resting (sitting) baseline (to establish the patients as their own controls), one minute of paced, deep breathing at 0.1 Hz (six breaths per minute, to stress the Parasympathetics), 1:35 minutes of Valsalva maneuvers (to stress the Sympathetics), and five minutes of head-up postural change (*i.e.*, standing, to document lightheadedness and SW, and the coordination between the P&S branches). These challenges are separated by baselines, and during each challenge, BP and HR was also measured. [5]

Morbidity risk is defined as either (1) two of the three Ewing Challenge (time Domain) ratios abnormally low or (2) resting P- or S-activity $< 0.5 \text{ bpm}^2$ [5]. Orthostatic dysfunction (whether Orthostatic Hypotension, Postural Orthostatic Tachycardia Syndrome, or Orthostatic Intolerance) is strongly associated with SW [5,7]. SW is a dysfunction of the alpha-adrenergic system causing insufficient vasoconstriction to support proper cardiac perfusion and thereby proper cerebral perfusion. SW is indicated when stand S-activity is less than resting S-activity, indicating risk of Orthostatic Dysfunction. Mortality risk is defined as either (1) all three Ewing Challenge ratios abnormally low or (2) resting P-activity $< 0.1 \text{ bpm}^2$ [5,8]. High mortality risk is indicated if resting P-activity $< 0.1 \text{ bpm}^2$ and $SB > 2.5$ (high SB, or high resting S-activity with respect to resting P-activity, indicates low

cardiac protection [9,10]). Baroreceptor Reflex (BRR) dysfunction is defined as a decrease in BP from rest to Valsalva. These are all quick, in-office measurements. All patients had a minimum of two follow-up tests (average number of tests = 4.8 and meantime between tests = 147.5 days). All HRV measures reported are computed based on the 1996 Standards established for HRV [11,12]. Exclusion criteria included: pregnancy, nursing, or refusal of autonomic testing. All patients consented to testing and patient data were maintained according to HIPPA guidelines.

RESULTS

Arguably the first and most debilitating symptom of autonomic dysfunction is lightheadedness due to Orthostatic Dysfunction [13,14], but is this just the beginning? In this study, we hypothesize that prolonged, untreated SW first leads to decreased Diastolic BP, eventually resulting in poor cardiac perfusion. This in turn leads to poor cerebral perfusion, which causes the brain to stimulate adrenaline release (“adrenaline storms”) to increase cardiac output. If prolonged, this continual or frequent stimulation leads to increased Systolic BP and a persistently increased cardiac workload. Persistently high Systolic BP with continued poor cardiac perfusion and cardiac function due to reduced Diastolic BP in turn leads to persistently increased Pulse Pressure. This is also associated with the onset of Cardiovascular Disease, including Hypertension, which is often difficult to manage due to poor cardiac and cerebral perfusion. Finally, this condition with persistent and untreated SW may lead to Heart Failure.

Table 1 describes the patient cohort. On average, patients were apparently healthy,

including BMI and HR within normal limits and BPs considered within normal limits for age. Upon standing, on average, patients' HR increased normally, as did their diastolic BP; however, the increase in their systolic BPs was weak. A weak increase in systolic BP upon standing indicates possible Orthostatic Intolerance, population wide. On average, nearly three-quarters of the population (71.7%) demonstrated BRR dysfunction. As the population aged, their average PP increased by 64.9%, putting the

average patient over 60 y/o with high or wide PP at risk for HF.

Table 2 presents the most prevalent diagnoses within the cohort at baseline. The age specific percentages indicate the distribution of patients by decade within that sub-group. The total percentages are based on the entire cohort. Therefore, 31.1% of the patients diagnosed with tachycardia were in their 50s, and 12.8% of the entire population were found to be tachycardic. While already under management, the

Table 1: Patient Demographics and resting and standing hemodynamics.

	Age (yrs)	N	%F	Ht (in)	Wt (#)	Bx HR	Bx sBP	Bx dBP	Bx PP	S HR	S sBP	S dBP
40 - 49	45.0	1273	59.8	66.7	200.0	76.4	124.3	77.6	46.7	85.6	125.6	81.4
50 - 59	54.8	2092	50.6	67.0	198.8	72.9	128.9	76.8	52.1	80.4	130.6	80.5
60 - 69	64.8	2770	46.8	67.4	197.8	70.0	132.2	72.9	59.4	77.1	134.0	77.0
70 - 79	74.0	2287	46.9	66.8	184.1	68.1	134.8	68.7	66.1	74.6	136.3	72.4
80 - 89	83.2	917	51.6	65.9	162.7	67.1	140.9	66.3	74.7	73.3	140.6	69.0
> 89	91.8	106	65.1	64.4	142.9	70.9	142.3	65.3	77.0	77.1	144.3	69.8
Total	68.9	9445	50.1	66.8	189.2	71.8	130.5	72.9	57.6	79.6	132.0	76.7

BP=Blood Pressure, BRR Dysf=Baroreceptor Reflex Dysfunction, Bx=Baseline, dBP=diastolic BP, F=Female, Ht=Height, HR=Heart Rate, N=Number, PP=Pulse Pressure, S=Stand (up-right postural change), sBP=systolic BP, Wt=Weight,

Table 2: Cohort diagnoses at baseline testing.

Age	% Tach	% Brad	% HTN	% HF	% MI	% DM2	% RI	% Dep	% LH	% Sm
40-49	20.3	16.2	9.5	0.0	0.1	15.1	0.1	14.0	17.9	16.8
50-59	31.1	23.8	21.3	6.4	4.2%	19.1	4.6	12.0	22.5	18.6
60-69	21.6	18.9	30.3	13.7	6.5%	21.8	5.2	10.7	26.9	21.7
70-79	6.8	18.4	20.9	14.8	7.2%	10.7	4.6	11.0	30.6	25.7
80-89	1.4	3.5	12.4	17.5	7.0%	7.9	8.2	8.9	36.5	12.4
>89	0.0	2.7	12.5	18.0	8.0%	8.0	8.0	8.0	30.0	1.3
Total	12.8	10.1	32.7	35.2	16.2	36.2	17.0	24.8	24.3	8.7

% = percent (all values are percentages); Tach = Tachycardia; Brad = Bradycardia; HTN = Hypertension; HF = Heart Failure; MI = Myocardial Infarction; DM2 = Diabetes Mellitus, Type 2; RI = Renal Insufficiency; Dep = Depression; LH = Lightheadedness or dizziness; Sm = Smoker. Total percentages based on entire population. Age range percentages based on individual parameter total. See text for details.

primary reason for baseline P&S Monitoring for 12.8% of the cohort was tachycardia and for 10.1% of the population was

bradycardia. The trend with age for the two are not significant ($p>0.15$). Hypertension (HTN) was the primary reason for P&S

Monitoring for 32.7% of the cohort, and HTN trended with age ($p=0.03$). Similarly, Heart Failure (HF) was the primary reason for P&S Monitoring for 35.2% of the cohort, and HF trended with age ($p=0.04$). Of the cohort, 16.2% were diagnosed as post-MI, which trended with age ($p=0.04$), and 36.2% were diagnosed with type 2 Diabetes (DM2), which also trended with age ($p=0.05$). Of the cohort, 17.0% were diagnosed with renal insufficiency (RI),

which trended with age ($p=0.04$). The trending with age for these diseases is significant. Depression and lightheadedness or dizziness were significant secondary disorders, presenting in 24.8% and 24.3% of the cohort, respectively; neither were significantly trended with age ($p>0.11$). Smoking was reported in 8.7% of the cohort and not correlated with age ($p=0.17$).

Table 3: Cohort medications at baseline testing.

Age	% β B	% β B3	% ACE	% ARB	% CCB	% VaD	% Diu	% α Ag	% β 2A	% Ach	% Sta
40-49	28.3	10.8	15.9	21.2	11.5	3.5	11.5	12.3	8.0	0.9	30.1
50-59	22.4	12.6	11.6	16.8	10.8	4.3	14.2	29.2	6.0	1.1	30.6
60-69	29.7	12.8	12.5	16.5	15.0	4.9	29.7	24.6	4.9	1.3	37.9
70-79	31.7	13.7	13.8	19.6	16.3	7.1	23.0	20.0	6.3	1.4	40.8
80-89	28.1	14.2	9.4	16.4	20.3	13.3	16.9	10.8	2.3	1.4	39.1
>89	28.6	13.1	0.0	14.3	0.0	0.0	0.7	0.0	0.0	0.7	14.3
Total	28.5	12.4	12.4	17.8	14.6	6.1	13.8	6.0	5.4	1.2	35.9

% = percent (all values are percentages); β B = Beta-Blocker; β B3 = Generation 3, Beta-Blocker; ACE = Angiotensin Converting Enzyme Inhibitor; ARB = Angiotensin Reuptake Blocker; CCB = Calcium Channel Blocker; VaD = Vasodilator, including α -blockers; Diu = Diuretic; α -Agonist; β 2A = Beta-2 Agonist; Ach = Anti-Cholinergic; Sta = Statin. Total percentages based on entire population. Age range percentages based on individual parameter total.

Table 3 presents the most prevalent medications prescribed to the cohort at baseline. The age specific percentages indicate the distribution of medications to patients by decade within that sub-group. The total percentages are based on the entire cohort. Therefore, 29.7% of the patients in their 60s were found to be prescribed beta-

blockers (β B), and 28.5% of the entire population was prescribed β B. The trending with age is not significant. This is so for all medications listed in Table 3. Third generation beta-blockers (*e.g.*, Carvedilol) were prescribed to 12.4% of the cohort, largely patients diagnosed with diabetes. Anti-hypertensives were prescribed: 12.4%

of the cohort was prescribed Angiotensin Converting Enzyme Inhibitors (ACEs), 17.8% of the cohort was prescribed Angiotensin Reuptake Blockers (ARBs), and 14.6% were prescribed Calcium Channel Blockers (CCBs). Vasodilators were prescribed to 6.1% of the cohort and diuretics to 13.8%. For Orthostatic Dysfunction associated with lightheadedness or dizziness, 6.0% of the cohort was prescribed alpha-agonists (*e.g.*, Midodrine). For COPD and other respiratory diseases associated with cardiovascular diseases (CVDs), 5.4% were prescribed beta-2 agonists (*e.g.*, Bronchodilators). Anti-cholinergics in the form of anti-depressants (*e.g.*, SSRIs) were prescribed to 1.2% of the cohort. Statins were prescribed to 35.9% of the cohort.

Patients' average Ejection Fractions (EF-a, Table 4) are within normal limits throughout the decades (60.8%) and trends significantly downward from youngest to oldest ($p=0.04$). Within the cohort, EF varies from 12% to 87%, with the lowest EFs generally lower for older patients ($p=0.03$). The highest EFs generally trend higher for older patients as well, however this is not significant ($p=0.09$). Both the FRS and RRS trend significantly higher with age ($p=0.04$, and $p=0.02$; respectively). BRR also trends significantly higher with age ($p=0.01$) and is prevalent throughout this population (average population prevalence = 48.3%).

DISCUSSION

As these two clinics manage both cardiovascular and P&S disorders, the prevalence of prolonged SW is significantly reduced as compared with practices that do not [personal communications]. However, SW is still a factor due to the fact that it is often the first P&S disorder to present and

Table 4: Cohort description and hemodynamics at baseline testing.

Age	EF-a	EF-l	EF-h	FRS	RRS	BRRd
40-49	62.7	25.0	83.0	9.0	0.0	41.6%
50-59	60.9	20.0	85.0	15.7	3.6	43.0%
60-69	59.8	12.0	82.0	20.8	10.6	47.5%
70-79	59.6	20.0	87.0	24.8	12.2	59.8%
80-89	60.9	21.0	84.0	27.0	29.5	67.7%
>89	50.5	46.0	55.0	24.8	32.1	70.0%
Total	60.8	12.0	87.0	19.4	17.6	48.3%

EF = Ejection Fraction (%); a = average; l = minimum (low); h = maximum (high); FRS = Framingham Risk Score (%); RRS = Reynolds Risk Score (%); BRRd = Baroreceptor Reflex Dysfunction. Total percentages based on entire population. Age

often the most difficult to relieve [13,14].

The HR, BP, and EF results indicate that this is a well-managed cardiology population, according to standards.

The most prevalent diseases are HTN, heart failure, and diabetes, with depression and lightheadedness or dizziness as the most prevalent comorbidities. Depression and lightheadedness are both confounding comorbidities. Depression is known to elevate mortality risk in heart disease patients [15]. Depression is often characterized by Parasympathetic Excess (PE). Dynamic PE (PE in response to S-challenges such as Valsalva or stand) is associated with depression-anxiety disorders, including Bipolar disease, Manic-Depression, and attention deficit disorders. Resting PE, as indicated by low SB, is associated with depression typically without anxiety. It was demonstrated that low SB (resting PE) with normal to low BP and HR may be induced by more sympatholytic than needed for that individual patient. Indeed, those patients' sympatholytic dosages were

moderate to high. For those patients, rather than introducing an anti-cholinergic agent, their sympatholytic dose was titrated lower against normal SB and normal BP and HR, thereby relieving their depression symptoms.

Lightheadedness, due to its contribution to falls, contributes to morbidity risk as well as mortality risk. Like depression, lightheadedness or dizziness also has many etiologies, including excess vagal activity (PE), poor brain perfusion (due either to syncope or Orthostatic Dysfunction, or both), low BP or HR, vestibular dysfunction, carotid stenosis, low blood volume, etc. Cardiovascular disease therapies target lower BP, for example, by lowering blood volume, which also lowers Sympathetic activity. From an autonomic balance (SB) perspective, low Sympathetic activity may induce high Parasympathetic activity or PE. PE is associated with poor brain perfusion, Vasovagal Syncope, and low HR. PE during stand may mask SW. SW often underlies Orthostatic Dysfunction. PE and SW are additional pieces of information that aid in diagnosing and treating lightheadedness [6, 16].

From Table 1, the cohort's average BP increases, albeit weakly, from rest to stand: 130.5/72.9mmHg to 144.3/69.8mmHg (a 10% increase is considered normal). Also, from Table 1, the mean HR increases normally from rest to stand: 71.8 bpm to 79.6 bpm. This magnitude of average change is similar across the ages. This indicates that the average patient in this cohort has a normal HR response to standing and does not have SW, and therefore does not have NOH. However, from Table 5, this cohort includes 56.1% of the patients who demonstrate SW. This is due to the fact that

those with SW had a smaller decrease in Sympathetic activity (LFa) upon standing than those without. Like BP, Sympatheti

Table 5: Patient P&S data and BP data.

	Bx LFa	Bx RFa	SB	S LFa	S RFa	% SW	% Low Bx dBP	% Hi Bx sBP	% Hi PP	% HF	% CAN	% SB>2.5
40 - 49	2.5	2.0	2.2	3.7	1.5	41.8	6.0	16.4	12.9	5.1	3.0	28.7
50 - 59	1.5	1.1	2.3	4.9	2.6	52.6	6.1	23.9	25.9	12.1	7.2	29.3
60 - 69	1.1	1.0	2.1	4.4	2.5	58.5	11.3	30.6	44.2	20.5	11.2	25.1
70 - 79	1.0	1.0	2.1	6.0	3.8	62.9	20.3	36.9	62.9	30.5	15.1	26.0
80 - 89	0.6	0.5	1.9	5.4	2.9	60.2	29.9	49.5	77.4	41.1	20.8	23.0
> 89	0.5	0.3	1.8	1.5	1.2	53.8	36.8	51.9	81.1	46.2	23.6	20.8
Total	1.2	1.0	2.1	4.3	2.4	56.1	24.5	53.4	75.0	56.3	18.6	48.6

BP=Blood Pressure, Bx=Baseline or rest, CAN=Cardiovascular Autonomic Neuropathy, dBP=diastolic BP, HF=Heart Failure, LFa=the Sympathetic measure Low Frequency area, N=Number, PP=Pulse Pressure, RFa=the Parasympathetic measure Respiratory Frequency area, S=Stand or up-right posture, SB=Sympathovagal Balance, sBP=systolic BP, SW=Sympathetic Withdrawal. See text for details.

activity is expected to increase approximately 10% upon standing. Therefore, any increase less than 10% is already abnormal. Yet, our definition of SW is a decrease in Sympathetic activity. This is both a legacy result and a practical result. The legacy is that Orthostatic Hypotension (a result of persistent SW and the most common form of Orthostatic Dysfunction) is defined as a 20/10 mmHg drop in BP upon standing. Like Sympathetic activity, BP is expected to increase by about 10/5mmHg. Again, therefore, any drop is already abnormal. Then patients have to wait until the drop is three times abnormal to receive therapy. It is hoped that the additional information of SW will enable earlier detection and treatment to improve patient outcomes.

Even in a seemingly well-managed cardiology cohort, SW is prevalent. Considering the hypothesis, Table 5 provides more insight. The percentages in

the columns to the right of the SW column (within the heavier outline) are percentages derived from the SW sub-population within this cohort (from the SW column itself), not the total population. Of the population with SW, approximately a quarter also have low resting diastolic BP (Bx dBP), and the numbers increase as SW persists ($p=0.023$). While many start with high resting systolic BP (Bx sBP), resulting from stress (including pain and anxiety) leading to hypertension, the increases in the numbers with high Bx sBP also track significantly with the persistence of SW ($p=0.041$). With persistent SW and persistently lower dBP and higher sBP, PP widens. Granted, the number of people remaining in the cohort after 70 y/o dwindle; regardless, the number with wide PP rises sharply. This rise is significant ($p=0.001$). As a result, those at risk for HF increase ($p=0.004$). The increased risk for HF is supported by the concurrent increases in CAN and high SB

which are additional MACE risk indicators ($p=0.014$ and $p=0.043$). Again, high sBP with high SB is also associated with stress (including pain and anxiety), leading to relatively high resting Sympathetic tone.

This is a reason why the significance of the high SB with age is less than the rest and similar to that of BP. Figure 1 graphically depicts our Hypothesis.

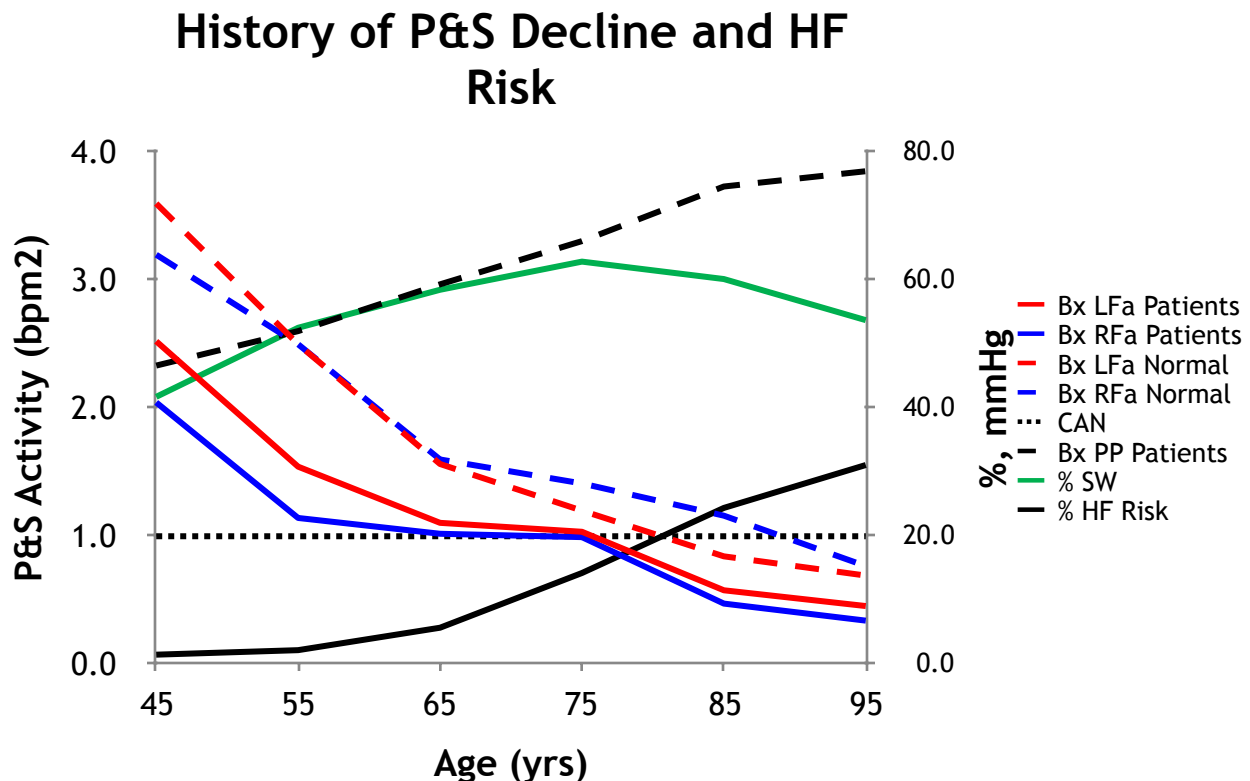


Figure 1: A depiction of the timing of P&S decline and the onset of HF. The data are normalized to P&S = 1.0 (dotted black line). This is the threshold for CAN. Below this threshold, cardiovascular mortality risk becomes significant, in correlation with the Framingham Heart Study Risk. As P&S activity (solid red & blue lines) declines more rapidly than that for normal subjects (broken red & blue lines), the prevalence (% of population) of SW increases (green line). Persistent SW leads to increases in PP (mmHg, broken black line). Persistent increases in PP eventually lead to increases in HF prevalence (% , solid black line).

CONCLUSION

These results indicate that this is a well-managed cardiology population, as supported by their normal HRs and EFs, on average, and the lack of significant

correlation between age and BP, in spite of the cohort's average BMI indicating that they are overweight. Significant EF, FRS, and RRS trending with age are not unexpected, regardless of management. Average EF and FRS have similar age-based

trends and statistical significance. The RRS trends higher than FRS and has greater statistical significance with age. The latter may be a result of the difference between the two scores, in that the RRS includes family history of CVD. Beta-blockers, anti-hypertensives, diuretics, and statins are the most-prescribed medications in this aggressively treated cardiology cohort.

Yet SW presents and persists, and even though the cohorts' P&S is being treated to relieve SW, SW may take as long as a couple of years to relieve, depending on duration of P&S dysfunction, patient history, and patient lifestyle (diet and exercise, including style and intensity of exercise).

REFERENCES

- 1 Hollenberg SM, Warner Stevenson L, Ahmad T, Amin VJ, Bozkurt B, Butler J, Davis LL, Drazner MH, Kirkpatrick JN, Peterson PN, Reed BN, Roy CL, Storrow AB. 2019 ACC expert consensus decision pathway on risk assessment, management, and clinical trajectory of patients hospitalized with heart failure: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2019;74:1966–2011.
- 2 Verdecchia P, Angeli F. Does brachial pulse pressure predict coronary events?. *Adv. Cardiol*. 2007; 44: 150-159
- 3 Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased Pulse Pressure and Risk of Heart Failure in the Elderly. *JAMA*. 1999;281(7):634–643. doi:10.1001/jama.281.7.634
- 4 Ferreira AR, Mendes S, Leite L, Monteiro S, Pego M. Pulse pressure can predict mortality in advanced heart failure. *Rev Port Cardiol*. 2016 Apr;35(4):225-8. doi: 10.1016/j.repc.2015.11.012. Epub 2016 Mar 19. PMID: 27006063.
- 5 Colombo J, Arora RR, DePace NL, Vinik AI. Clinical Autonomic Dysfunction: Measurement, Indications, Therapies, and Outcomes. Springer Science + Business Media, New York, NY, 2014.
- 6 Arora RR, Bulgarelli RJ, Ghosh-Dastidar S, Colombo J. Autonomic mechanisms and therapeutic implications of postural diabetic cardiovascular abnormalities. *J Diabetes Science and Technology*. 2008; 2(4): 568-71.
- 7 DePace NL, Vinik AI, Acosta C and Colombo J. Oral vasoactive medications: A Review of Midodrine, Droxidopa, and Pseudoephedrine as Applied to Orthostatic Dysfunction. 2020. Submitted.
- 8 Murray GL, Colombo J. Routine Measurements of Cardiac Parasympathetic and Sympathetic Nervous Systems Assists in Primary and Secondary Risk Stratification and Management of Cardiovascular Clinic Patients. *Clin Cardiol Cardiovasc Med*. 2019; 3(1): 27-33. <https://doi.org/10.33805/2639.6807.122>.

- 9 Umetani K, Singer DH, McCraty R, and Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades. *JACC*. 1998; 31(3), 593 – 601.
- 10 Curtis BM, O’Keefe JH. Autonomic tone as a cardiovascular risk factor: The dangers of chronic fight or flight. *Mayo Clin Proc*. 2002; 77:45-54.
- 11 Malik, M. The 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*. 1996; 93:1043-1065.
- 12 Malik, M. and the 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. *European Heart Journal*. 1996, 17: 354-381.
- 13 Vinik AI, Maser RE, Nakave AA. Diabetic cardiovascular autonomic nerve dysfunction. *US Endocrine Disease*. 2007; Dec: 2-9.
- 14 Vinik A, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation*. 2007; 115: 387-397.
- 15 Litchman JH, Bigger JT Jr, Blumenthal JA, et al. Depression and coronary heart disease recommendations for screening, referral, and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. *Circulation*. 2008; 118: 1768-1775.
- 16 Tobias H, Vinitzky A, Bulgarelli RJ, Ghosh-Dastidar S, Colombo J. Autonomic nervous system monitoring of patients with excess parasympathetic responses to sympathetic challenges – clinical observations. *US Neurology*. 2010; 5(2): 62-66.