

Autonomic Dysfunction in Migraine: A Case Study

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INTRODUCTION

It is believed that there are approximately 28 million migraine sufferers in the US alone.¹ A significant portion of many neurology practice populations includes these headache patients. It is suspected that there is an autonomic component to migraine.^{2,3,4} Autonomic nervous system (ANS) changes in migraineurs, however, have not been completely studied to date. Clearly, these changes exist, as migraine patients commonly describe symptoms of ANS dysfunction before, during and after migraine headaches. These include presyncope, diaphoresis, yawning, polyuria and mood changes. Autonomic involvement also seems reasonable given the importance and role of the ANS in the coordination and control of homeostasis, and the body's response to stress and injury. We present a case that was studied using ANS monitoring technology in a migraineur.

METHODS

A patient with known migraine without aura was studied using ANSAR technology (Philadelphia, PA) interictally when totally free of migraine symptoms. During the prodrome, he was re-tested just as the prodrome was ending and mild headache was beginning. Two hours after migraine onset he was injected with sumatriptan 6 mg subcutaneously when pain was moderately severe. This resulted in resolution of all migraine symptoms in less than one hour. He was re-tested at approximately 70 minutes and at 7 hours after treatment with subcutaneous sumatriptan.

The ANS monitoring technology used provides a noninvasive, independent and real-time quantitative measure of both branches of the ANS. It was the patented and FDA approved ANX3.0 ANS monitor from ANSAR, Inc. (Philadelphia, PA). The monitor is based on spectral analyses of heart rate variability (HRV) and respiratory activity (RA). The analysis of RA provides a marker for determining vagal activity and thereby indicating parasympathetic influence on HR control. With parasympathetic (respiratory frequency area – RFa) activity identified from the HRV spectrum, sympathetic activity is then determined from the remaining HRV spectral components that define the scope of sympathetic function (low frequency area – LFa).^{5,6,7,8}

The clinical exam is comprised of six phases that challenge and record ANS responses at rest, to individual parasympathetic and sympathetic challenges (deep breathing and a series of short Valsalva maneuvers, respectively) and to a system challenge (quick postural change, followed by continuous, quiet upright posture). These four challenges are separated by two intervening baseline episodes to allow the ANS to settle. The six

phases are, in order: 1) a 5-minute resting initial baseline, 2) a 1-minute period of relaxed deep breathing at 6 breaths per minute, 3) a 1-minute baseline, 4) a 1 minute 35 second period of 5 short Valsalva maneuvers, 5) a 2-minute baseline and 6) a 5-minute stand period. Mean HR, range HR, the fundamental respiratory frequency (the FRF: approximately the mean breathing frequency), the LFa (the sympathetic measure), the RFa (the parasympathetic measure), the LFa/RFa ratio (a measure of sympathovagal balance), and noninvasive blood pressure (NIBP: 1 per phase) were averaged or measured per exam phase, along with the continuous measures of EKG, and instantaneous HR, RA, LFa and RFa. The EKG and RA were measured using a standard FDA approved bedside monitor. A typical normal patient response to the clinical exam is shown in Figure 1.^{9,10}

CASE HISTORY

The patient was a 57-year-old, healthy, fit male, 5'7" tall, 160 lbs., with a history of migraine without aura (IHS 1.1) since age 8. At the time of ANS testing, the patient's migraine frequency varied from 0 to 3 per month (2-per-month average). These headaches would often be preceded by a prodrome lasting several hours, consisting of mood change, fatigue, yawning and polyuria. The headache would usually start anteriorly (either side) and gradually increase in severity over the course of 1 to 2 hours. Typically, maximum headache intensity would occur roughly 2 hours after the onset if left untreated. It would then develop into a throbbing pain with nausea (rarely vomiting) and photophonophobia. It was also worsened by movement. His headaches were exquisitely responsive to triptans, used either orally, intranasally or subcutaneously. In fact, all 7 currently available triptans have been shown to be effective in this patient. The only comorbid conditions were mild controlled hypercholesterolemia (treated with atorvastatin 10 mg per day) and rare episodes of presyncope, secondary to orthostasis. There was no history of any cardiac problems, confirmed by an exercise stress test done 3 years prior. There was no history of hypertension or diabetes. Family history revealed that the patient's father had a history of migraine without aura. The patient's sister also had occasional migraine. All three of the patient's children had a history of migraine without aura.

CASE STUDY

The patient currently uses oral or subcutaneous sumatriptan when needed. Migraines tend to last 4 to 12 hours when untreated and when treated with subcutaneous sumatriptan are promptly aborted in less than 30 minutes. For this particular case study, the patient was interictally tested using ANS monitoring 3 days before a spontaneous attack. On the day of the attack, he was seen in the office while still prodromal and was serially tested at migraine prodrome and migraine onset, prior to sumatriptan dosing when headache was severe and after sumatriptan dosing.

ANS Study #1: Interictal Study

From the interictal ANS test (see Figure 2), his HR chart shows no abnormalities. His trends plot (a plot showing the instantaneous LFa and RFa values throughout the clinical exam) shows some weakness in his sympathetic responses to Valsalva challenge. The average, age-adjusted RFa and LFa responses to challenge (deep breathing and Valsalva,

respectively) are normal. Stand response does show some abnormality indicating paradoxical parasympathetic syndrome (PPS), with sympathetic withdrawal. Sympathetic withdrawal is confirmed by the fact that the LFa decreases from sitting to standing, from 5.18 bpm² down to 3.98 bpm². Sympathetic withdrawal is suggestive of orthostasis. PPS is documented by the fact that his RFa goes from 3.22 bpm² during initial baseline up to 4.04 bpm² upon standing. This is an abnormal parasympathetic increase to a sympathetic challenge: standing. His Valsalva parasympathetic response, however, is within normal parameters.

His baseline numbers of 5.18 bpm² for the LFa and 3.98 bpm² for the RFa are well within the normal range and showing a normal sympathovagal balance of 1.61. His BP does drop from sitting to standing 130/75 down to 113/82 mmHg. This drop in BP combined with the sympathetic withdrawal indicates possible orthostatic hypotension. Upon questioning, the patient did report occasional dizziness upon standing and that dizziness does increase in frequency when a migraine is near or during a migraine attack. Although the patient does present with PPS, he does not show excess vagal activity throughout the test. There is also a potential for syncope given that his peak sympathetic LFa response to Valsalva shown in the trends plot is not greater than twice the first peak of his sympathetic response to stand. This has been found in other patients to be suggestive of presyncope or syncope. In summary, the patient at rest in a non-migraine state is relatively normal with excess dynamic parasympathetic activity which can be contributing to his orthostasis as well as his potential presyncopal state.

ANS Study #2: Migraine Prodrome/Initial Pain Onset Study

On the day of testing, the patient presented with a migraine prodrome with slight migraine pain starting while the study was in progress. His ANS test (see Figure 3), which was administered at 8:43 a.m. shows normal baseline ANS responses, normal parasympathetic responses to deep breathing, normal HR and normal HRV; comparable to his interictal baseline ANS study 3 days previous. Although his average sympathetic response to Valsalva is in the normal range, his peak sympathetic activity during Valsalva is excessive with elevated parasympathetic activity at Valsalva (PPS) as compared to his interictal ANS study. The patient continues to manifest PPS during his stand response. His RFa baseline is 3.56 bpm² and increases to 4.25 bpm² upon standing. The significant difference between the interictal study and this one is that his overall Valsalva response is no longer normal. His Valsalva RFa is 10.58 bpm² showing an almost threefold increase from baseline, whereas before it was normal (less than a twofold increase).

PPS is known to cause excess sympathetic activity at Valsalva (a hypersympathetic response). The excess sympathetic activity has been found to be secondary to PPS. The hypersympathetic response in this case may also include a pain response (pain is a sympathetic stressor). The hypersympathetic response and the PPS in this study seem to mask the orthostasis present in the interictal study. His sympathetic withdrawal is no longer evident, however his BP still decreases in this study from 132/90 to 116/88 mmHg. The patient's baseline numbers are LFa 2.35 bpm², RFa 3.56 bpm², showing much more vagal activity at baseline as indicated by the fact that his ratio, while still in the normal range (0.4 to 3.0 bpm²), has dropped to 0.66 bpm². Overall, as compared to

the baseline study, the patient is showing a significant increase in parasympathetic activity throughout the study. From his Valsalva response, this increased parasympathetic activity may also be elevating his pain sensitivity.

ANS Study #3: Fully Involved Migraine Study, Pre-Treatment – Severe Pain

Approximately two hours later, at 10:20 a.m., just before sumatriptan dosing, the patient was complaining of a full-blown migraine with mild photophonophobia, slight nausea and severe unilateral throbbing pain. At this point, although the patient's baseline ANS responses, average parasympathetic response to deep breathing, average sympathetic response to Valsalva, HR and HRV responses are still normal, (see Figure 4) his trends plot shows that the overall Valsalva response continues to be poor. The instantaneous sympathetic peak response to Valsalva is off the scale and the Valsalva parasympathetic activity remains excessive. The patient's baseline numbers, however, have become sympathetically dominant: his sympathetic (LFa) response at baseline is 3.96 bpm² and his parasympathetic (RFa) response at baseline is 2.27 bpm², leading to a ratio (sympathovagal balance) of 1.74. Although these baseline values are all normal, it is the inverse of his interictal state. This indicates that the patient is no longer vagal at baseline, he is normal in the sense that he has sympathetic dominance at baseline. However, this may be suggestive of the fact that his pain levels are higher causing the sympathetics to increase both at rest and in response to challenge.

The patient still maintains a greater than twofold increase in his RFa at Valsalva (one indication of PPS) from 2.27 bpm² at baseline to 5.55 bpm² during Valsalva. Also, he continues to have an increase in parasympathetic (RFa) response to stand (the other indication of PPS – only one is necessary) as compared to baseline; his RFa at baseline is 2.27 bpm² to 2.65 bpm² upon standing. The patient, upon standing in this test, manifests orthostasis again where his sympathetic (LFa) response decreases (indicating sympathetic withdrawal and suggesting orthostasis) from 3.96 bpm² down to 3.13 bpm². To summarize, except for the extra pain causing more sympathetic response at baseline, the patient is essentially in the same state as 2 hours earlier when the pain was mild and the migraine was just beginning.

ANS Study #4: Fully Involved Migraine Study, 70 minutes Post-treatment – Symptom Free

Upon completion of the second ANSAR ANS test, the patient was dosed at 10:35 a.m. with 6 mg sumatriptan subcutaneously. Approximately 70 minutes later, at 12:07 a.m. (post-dosing) the patient reports being totally pain and symptom free and submitted to a third ANS test for the day (see Figure 5). However, this third ANS test indicates persisting ANS changes, suggesting that his pain and symptoms might be masked at this time. On his third ANS test of the day, his HR, HRV, baseline ANS results and parasympathetic response to deep breathing are all normal. Again, his sympathetic response to Valsalva is off the scale, although it looks like the parasympathetic response to Valsalva has decreased. His baseline numbers have gone back to his normal vagal dominance, his sympathetic (LFa) response at baseline is 1.83 bpm², and his parasympathetics (RFa) response at baseline is 3.15 bpm² with a sympathovagal balance at baseline of 0.58. Although it is normal, it is on the low end of normal.

His parasympathetic (RFa) response to Valsalva is only 4.91 bpm² which is well within the range of normal (< 100% increase over baseline) and his parasympathetic (RFa) response at stand is 3.07 which is within the borderline range for PPS (< 10% increase over baseline). Thus, his PPS has normalized, but the hypersympathetic effect still lingers. His sympathetic (LFa) response to stand does decrease from seated baseline, from 1.83 bpm² down to 1.64 bpm², but his BP increases a slight amount this time from 128/89 to 130/88 mmHg, suggesting that the orthostasis is being corrected.

In summary, 70 minutes after sumatriptan dosing the patient's ANS test shows that most of the pre- and post-migraine ANS changes have normalized or are at least in their respective borderline ranges. There is only a mild hypersympathetic response with sympathetic withdrawal lingering. This correction is possibly a response to sumatriptan therapy or, perhaps, to underlying persisting brainstem sympathetic activation.

ANS Study #5: Migraine Study, 7 hours Post-Treatment

The final test of the day was taken 7 hours post-sumatriptan dosing at around 5:17 p.m. According to the ANS test (see Figure 6), the patient's HR and HRV are normal. His ANS baseline response, parasympathetic response to deep breathing and his sympathetic response to Valsalva are normal. His stand response is still abnormal however similar to his interictal baseline, his peak sympathetic response to Valsalva is back down to what seems to be normal for him, slightly low according to the general population in his age range. His baseline numbers are back to near his interictal baseline, normal of LFa at 3.99 bpm², RFa at 2.74 bpm², and his sympathovagal balance being 1.46. His parasympathetic (RFa) response to Valsalva is 5.73, quite near the 100% increase allowable; and, his parasympathetic (RFa) response at stand is 2.62, showing a normal decrease. Also, his sympathetics do not withdraw and his blood pressure does increase from 121/86 to 127/82 mmHg.

The patient continued to report being pain and symptom-free. Therefore, it seems as if the sumatriptan was able to relieve the pain and symptoms within 70 minutes of subcutaneous dosing and resolve the ANS imbalances created by the migraine within 7 hours. It appears to take somewhat longer for the patient's ANS to return to its interictal baseline levels. Most of the return is accomplished within a substantial interval after the patient has experienced relief.

CONCLUSIONS

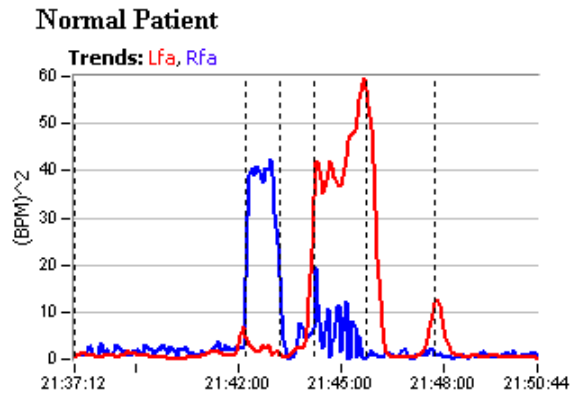
The fact that the patient presents with PPS, orthostasis and possible presyncope, suggest that the patient is vagally predisposed interictally. His vagal predisposition may be an underlying feature of his migraines. From this series of testing it also seems as if the parasympathetic response to Valsalva may be useful to quantify severity of migraine and track the recovery of the migraine post-therapy. Since the hypersympathetic activity occurs as a result of the paradoxical increase in parasympathetic activity, this suggests that it might be sympathetically mediated pain that the patient experiences during a migraine. The persistence of autonomic dysfunction 70 minutes after treatment and while the patient was symptom-free interestingly correlates with Weiller, et al's observation of

persisting upper brainstem activation during a migraine studied with PET scanning.¹¹ Of course, these observations are all conjectural and more studies need to be done. This particular case study tells a very neat and concise story and, as a template, may provide the basis for studying autonomic dysfunction in migraineurs.

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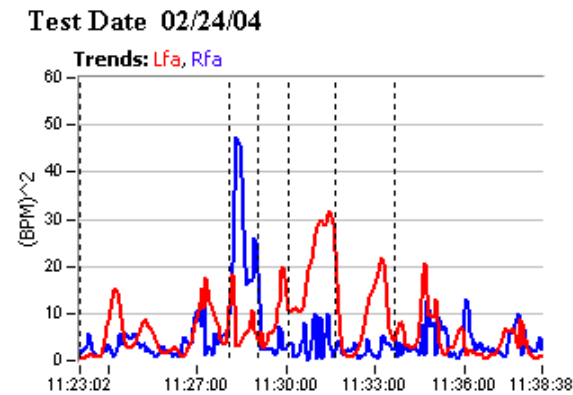
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FIGURES



	Event	mHR ¹	LFA+	RFA+
A	Baseline	65	0.78	1.79
B	Deep Breathing	68	2.03	39.74
C	Baseline	62	2.55	3.42
D	Valsalva	69	48.27	3.60
E	Baseline	66	0.77	0.83
F	Stand	72	0.59	0.72

Figure 1: An otherwise known healthy patient, a female, 44 years of age. This can be used for comparison.



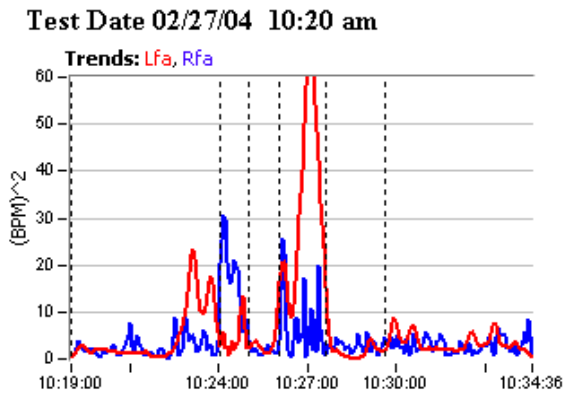
	Event	mHR ¹	LFA+	RFA+
A	Baseline	76	5.18	3.22
B	Deep Breathing	73	5.34	30.72
C	Baseline	77	8.39	3.13
D	Valsalva	74	27.48	4.39
E	Baseline	75	9.14	1.82
F	Stand	82	3.98	4.04

Figure 2: ANS Study #1, The case study's interictal study.

Test Date 02/27/04 8:43 a.m.

	Event	mHR	LFA+	RFA+	LFA/RFA	BP
A	Baseline	69	2.35	3.56	0.66	132/90
B	Deep Breathing	66	4.71	24.31	0.19	126/79
C	Baseline	72	2.69	2.11	1.27	126/84
D	Valsalva	66	39.74	10.58	3.76	121/80
E	Baseline	74	1.98	1.00	1.92	123/87
F	Stand	74	3.48	4.25	0.82	116/88

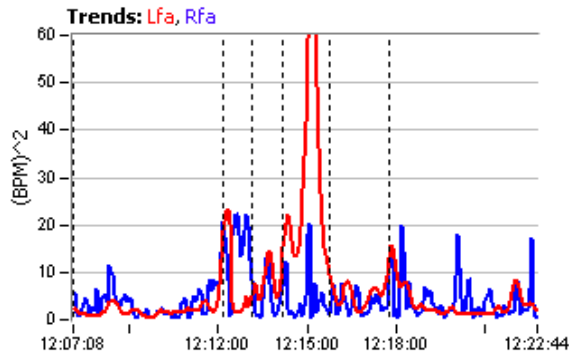
Figure 3: ANS Study #2, The case study's prodrome study.



	Event	mHR'	LFA+	RFA+
A	Baseline	69	3.96	2.27
B	Deep Breathing	65	4.47	16.78
C	Baseline	71	2.08	1.69
D	Valsalva	67	47.47	5.55
E	Baseline	71	1.05	2.74
F	Stand	75	3.13	2.65

Figure #4: ANS Study #3, fully involved migraine study, prior to treatment.

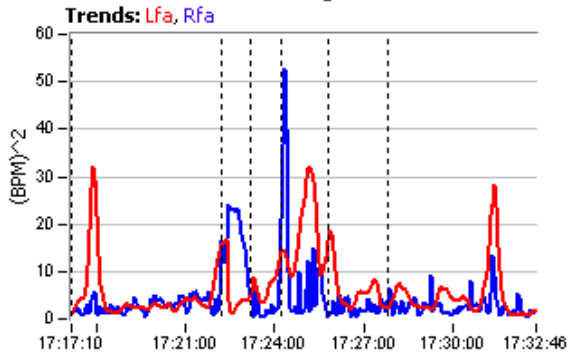
Test Date 02/27/04 12:07pm



	Event	mHR ¹	LFA+	RFA+
A	Baseline	71	1.83	3.15
B	Deep Breathing	69	4.43	16.70
C	Baseline	73	9.21	5.04
D	Valsalva	71	41.62	4.91
E	Baseline	71	4.71	3.55
F	Stand	77	1.64	3.07

Figure 5: ANS Study #4, fully involved migraine study, 70 minutes post- treatment.

Test Date 02/27/04 5:17pm



	Event	mHR ¹	LFA+	RFA+
A	Baseline	80	3.99	2.74
B	Deep Breathing	78	2.67	21.51
C	Baseline	84	5.77	1.58
D	Valsalva	77	21.86	5.73
E	Baseline	82	4.70	2.32
F	Stand	86	5.59	2.62

Figure 6: ANS Study #5, migraine study, 7 hours post- treatment.