COMPARING WATER IMMERSION SKIN WRINKLING AND TILT TABLE TESTING IN A YOUNG HEALTHY POPULATION

A Thesis
by
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Abstract

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Tilt table testing (TTT) is the golden standard in evaluating vasovagal syncope, an autonomic function. Water immersion skin wrinkling (WISW) has recently been linked to autonomic function. The purpose of this study is to compare WISW and TTT in a young healthy population. Six subjects (male n=3, female n=3) were admitted to Charleston Forge Vascular Laboratory for testing. Subjects were randomized into groups starting with TTT and WISW. TTT consisted of 5 minutes supine monitoring, followed by 5 minutes of 80° tilting, finishing with 5 more minutes of supine monitoring. WISW was administered by placing a subject's hand in lukewarm water for 20 minutes. Heart rate variability (HRV) was recorded for TTT and degree of wrinkling was recorded for WISW. A two-tailed t-test determined that there is not a significant difference between WISW and TTT.

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Correlating Water Immersion Skin Wrinkling and Tilt Table Testing in a Young Healthy Population

Chronotropic Incompetence (CI) is defined as the inability of the heart to compensate for an increase in activity. This may be suggestive of cardiovascular disease and is associated with increased mortality. CI is generally diagnosed with maximum exercise testing when the heart rate fails to reach 80% of age predicted values (Brubaker & Kitzman, 2011). While this is the most common way of diagnosing CI, other methods exist that are targeted to a specific population, such as the use of postural changes and blood pressure responses to investigate chronotropic incompetence, which gives insight into the autonomic regulation of a subject. Another way of diagnosing CI is blood pressure changes that occur with postural changes, in clinical populations performing max exercise testing may be difficult. Therefore, other autonomic tests such as cold pressor testing, water immersion skin wrinkling, and tilt table testing (TTT) should be studied to determine possible correlations in diagnosing CI.

Studies have shown that water immersion skin wrinkling is correlated to autonomic function (Teoh, Chow, & Wilder-Smith, 2008). Immersing hands or feet into water tends to cause wrinkling of the skin (Kamran, Salciccioli, & Lazar, 2010). It is hypothesized to occur due to vasoconstriction of palmar skin vasculature Barneveld, Palen, and Putten, (2010) were able to show that WISW is related to autonomic function, and wrinkling is graded on a clinical scale. Water immersion is a non-invasive test graded from 0-5 that involves placing one's hands into lukewarm water for a set amount of time and has proven to be clinically valuable in diagnosing certain diseases such as cystic fibrosis (Arkin et al., 2012). However,

water immersion testing is still novel and should be studied in depth to determine if there are any more clinical benefits or autonomic correlations.

Tilt table testing is used to evaluate unexplained syncope and heart rate variability (HRV), a predictor of mortality (Alvarez, Asensio, Lozano, Alvarez, & Portos, 2000). However, complications can arise upon tilting such as fainting, extreme discomfort, or even death. Subjects are placed on a tilt table and tilted to different positions, with blood pressure and heart rate responses being continually recorded. This process can be even more dangerous in a clinical population (Shinohara et al., 2014). Therefore, a prescreening test should be used to determine if TTT is needed (Shinohara et al., 2014).

HRV is a method of evaluating CI and autonomic function. HRV is defined as the heart's inability to compensate for an increase in activity (American Heart Association). Low HRV is associated with an increase in mortality (Brubaker & Kitzman, 2011). Multiple tests are used to evaluate HRV such as TTT. WISW is the least invasive and most feasible way to determine autonomic function (Barneveld, Palen, & Putten, 2010). The purpose of this study is to compare WISW and TTT. If a correlation exists, WISW will prove to be a valuable tool to determine if TTT is needed.

Review of Literature

Autonomic Function and Testing

The autonomic nervous system is critical for homeostasis in the body, as it controls heart rate and blood pressure. There are multiple tests for evaluating autonomic functions such as cold pressor testing, TTT, and water immersion skin wrinkling. These tests are non-invasive and provide valuable information about the autonomic system. It is important to use

multiple tests when determining autonomic function, as different tests elicit different autonomic responses (Hotta & Uchida, 2010). Abnormalities in testing are useful in diagnosing cardiovascular pathologies (Pautasso et al., 2014). When administering any autonomic tests it is crucial that the subject abstain from caffeine, nicotine and alcohol, as these substances may elicit autonomic responses.

Autonomic function may change with age. As aging occurs, fluctuations in heart rate and blood pressure can be seen due to inactivity, atherosclerosis, or other factors. A water immersion study using three different water temperatures of water revealed that older subjects experience a similar increase in heart rate and blood pressure as their younger counterparts (Hildenbrand, Becker, Whitcomb, & Sanders, 2010). A study from Kim and Nam (2010) using medical students demonstrated that older students had more sympathetic and less parasympathetic activity than their younger counterparts. The authors hypothesized that this phenomenon may occur due to increased financial, emotional, and family stress. With both tests revealing different results, other tests need to be conducted to determine if the autonomic system changes with age.

Cold Pressor Test

The cold pressor test is a non-invasive way to determine autonomic function (Silverthorn & Michael, 2013). The test is administered by submerging a subject's hands (up to the wrist) or feet (up to the ankle) in cold water for a designated period of time. A recent study has shown that the abrupt change in temperature associated with water immersion is the stimulus to autonomic response (Garg, Kumar, & Singh 2010). Thus, the temperature of

water should be monitored to elicit proper results. The body responds to cold water immersion by constricting the extremities to supply blood to the heart (Santarcangelo et al., 2013). It is common for subjects to feel pain or discomfort when hands or feet are submerged in cold water (Santarcangelo et al., 2013). Recent evidence suggest that the cold pressor test is multifactorial (Hildenbrand, Becker, Whitcomb, & Sanders, 2010). A study from Silverthorn and Michael (2013) revealed that white males and black males responded differently to testing, with black normotensive males experiencing a greater parasympathetic response and concluding that autonomic function may be determined by race. During testing, subjects should experience an increase in heart rate as well as an increase in blood pressure (Pautasso et al., 2014). Abnormalities in testing may suggest cardiovascular disease or other autonomic dysfunction (Pautasso et al., 2014).

Evidence suggests that hypertensive subjects respond to cold pressor testing to a greater degree than the average population (Wood, Sheps, Elveback, & Schirger, 1984). Garg et al. 2010 illustrated this by administering the cold pressor test to 100 students with normotensive parents and 100 students with hypertensive parents. Students with hypertensive parents experienced significantly higher rises in systolic and diastolic blood pressures within 30 seconds of immersion than students with normotensive parents. These finding suggest than an abnormal increase in blood pressure may be indicative of future hypertension. Furthermore, Barnett, Hines, Schirger, and Gage (1963) conducted a study to determine the development of a hyperreactive response to the cold pressor test across a 27 year span. The test concluded that some of the subjects who had a hyperreactive response to testing developed hypertension, while none of the subjects with a normal response developed

hypertension. Thus, cold pressor testing may be beneficial for diagnosing early autonomic dysfunctions.

Cold pressor tests can be used to determine heart rate variability. Recent evidence suggest that small heart rate variability is correlated with increased cardiac mortality. A study from Santarcangelo et al. (2013) determined that the immersion of hands in very cold water (0°) for up to 4 minutes led to a decreased R to R interval (the distance between two consecutive R waves on an EKG strip), which in turn, leads to an increased heart rate. Overall, the cold pressor test proves to be valuable in evaluating autonomic function (Barnett, Hines, Jr., Schirger, & Gage, 1963; Kasagi, Akahoshi, & Shimaoka, 1995; Pautasso et al., 2014; Santarcangelo et al., 2013; Wood, Sheps, Elveback, & Schirger, 1984).

Tilt Table Testing

TTT is a valuable tool in assessing orthostatic responses to postural changes without skeletal muscle pump (Alvarez et al., 2000). The primary use for TTT is to determine how individuals respond to orthostatic stress. A positive test occurs when the subject responds with a decrease in heart rate and/or blood pressure, while a negative test indicates that the body is responding normally (American Heart Association). This test is administered by first strapping a subject securely to the tilt table. The subject then undergoes a series of postural changes for designated time frames to determine how the autonomic nervous system responds (Leiria et al., 2013). Blood pressures and heart rates are monitored at each positon of the tilt, with the greatest responses seen within a minute of tilting. The baroreceptors that sense pressure changes in the body quickly respond, and an increase in blood pressure,

cardiac output, and heart rate is seen (Alvarez et al, 2000). Subjects with orthostatic intolerance or vasovagal syncope may feel discomfort, lightheadedness, or even pass out during the postural change with TTT. Therefore, it is critical to monitor the subject when changing positions by asking questions and recording heart rates and blood pressures.

The tilt table test can be used to determine vasovagal syncope (American Heart Association). Vasovagal synocope is a condition that causes blood vessels in the legs to dilate when moving to an upright position, which in turn causes a decrease in heart rate and blood pressure (Mathur, Guertin, Coleman, Thompson, & Kluger, 2013). Mathur et al. (2013) determined that subjects with high levels of physical activity were likely to experience vasovagal syncope. With exercise, blood vessels become larger in radius. This increase in radius makes it harder for the body to return blood to the brain with a postural change. This will cause the blood to pool in the legs, which may lead to fainting due to insufficient blood supply to the brain.

Different variables, such as gender or body mass index, may influence the outcome of TTT. Leiria et al. (2013) illustrated this occurrence by administering tilt table tests on overweight and underweight subjects. The underweight subjects were much more likely to experience a negative reaction to testing (Leiria et al. 2013). Furthermore, Mellingsaeter, Wyller, Wyller, and Ranhoff (2013) determined that elderly men were more likely to display symptoms of orthostatic intolerance than elderly women. Thus, there are different variables that may influence autonomic function and testing, and these variables should be more thoroughly studied (Shinohara et al., 2014).

Generally, approximately 10 minutes was considered to be the appropriate time at each tilting position to yield sufficient results. However, the necessary duration of TTT has

recently been challenged. A study from Alvarez et al. (2000), suggests that heart rate fluctuations early in testing can determine the outcome of the test. Testing for shorter periods of time allows for more subjects in a lesser amount of time, as well as less discomfort to the subject. The data from Alvarez et al. (2000) suggest that a positive test can be determined within the first five minutes of testing.

Overall, the tilt table test is valuable in determining autonomic function. The test is fairly noninvasive, though it may cause discomfort. There are a variety of conditions that can be determined using the tilt table. While the test is thoroughly studied, different variables that elicit changes during testing should be extensively researched, and due to the somewhat dangerous outcomes of the test, a prescreening test should be used to determine if TTT is needed.

Water Immersion Skin Wrinkling

Wilder-Smith and Chow (2002) determined that the physiologic process associated with water immersion skin wrinkling begins with digital vasoconstriction. According to Wilder-Smith and Chow (2002), skin wrinkling only occurs in glabrous digits because the tubular structure allows it. The dermal layer under the epidermis allows the digits to wrinkle easily. Glabrous bodies are connected to the epidermis and lose volume through vasoconstriction. This creates a pressure gradient that allows the skin to pull downward and wrinkle.

Abnormal WISW has been linked to different sympathetic dysfunctions. Ng et al. (2013) found that WISW could be used to determine sympathetic limb dysfunction, as

WISW was able to diagnose diabetic neuropathy. Multiple studies have shown that WISW is a valuable test in diagnosing cystic fibrosis (Arkin et al., 2012). Subjects who have cystic fibrosis wrinkled at an accelerated rate compared to a healthy population of the same age. Furthermore, Clark, Pentland, Ewing, and Clarke (1984) found that subjects with diabetes wrinkled at a slower rate than their healthy counterparts. The mechanisms behind these phenomena still need to be verified. Therefore, WISW mechanisms should be thoroughly studied to make possible correlations with other diseases, due to the feasibility and noninvasive nature of the test.

WISW has been linked with autonomic dysfunction. A study from Kamran, Salciccioli, and Lazar (2010) suggested that reduced WISW is correlated with heart failure. WISW has been shown to diagnose small fibre neuropathy and can be used for predicting intraepidermal nerve fibre density (Teoh et al, 2008). Thus, it is theorized that WISW is related to more distal portions of the autonomic nervous system. Therefore, it is important to combine WISW with other tests to determine if multiple forms of autonomic dysfunction exist.

Overall, WISW is a noninvasive feasible way to assess autonomic dysfunction. This test is easily administered and available virtually everywhere. WISW may be able to predict multiple disorders, including cystic fibrosis. The validity of WISW as a definitive predictor of autonomic function needs to be confirmed and compared to other autonomic tests.

Methods

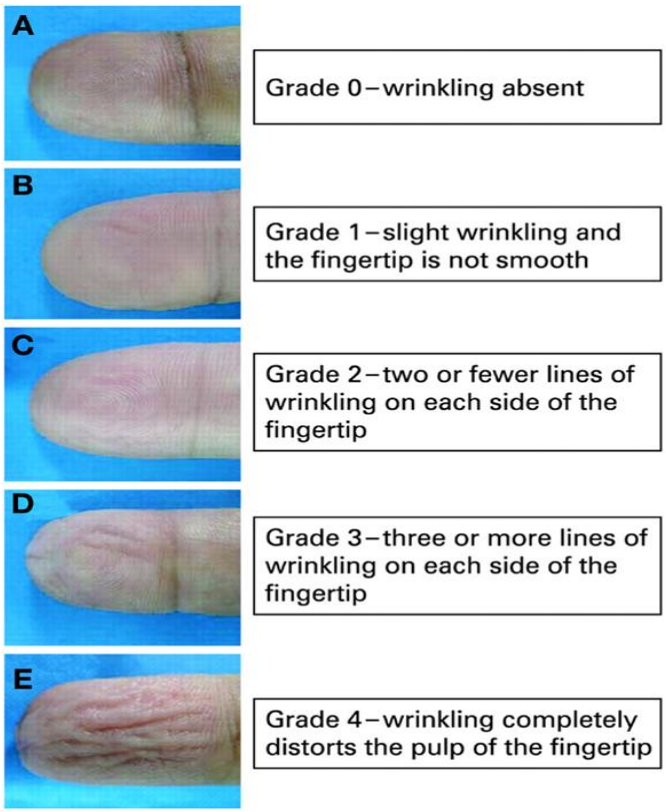
Subjects

Upon arrival Charleston Forge Vascular Biology and Autonomic Studies Laboratory, subjects' height, weight, and blood pressure were taken. Subjects (male n=3, female n=3) were asked to abstain from caffeine, nicotine, and alcohol 12 hours prior to testing. The subjects were educated on the risks and benefits of this study before signing consent forms. Subjects were placed into groups which determined order of testing. Appalachian State University's Institutional Review Board (IRB) approved this study.

Water Immersion Skin Wrinkling

The subject's left hand was placed in 25±1°C tap water for 20 minutes to elicit wrinkling. Subjects were asked to sit in a chair and place their hand (up to wrist) in a bucket in an adjacent seat. Water was kept at a constant temperature by stirring with a temperature probe. Pictures of wrinkling were taken with a 21 megapixel camera from a Motorola Droid Turbo. Wrinkling was graded based on a scale from Teoh et al. (2008).

Wrinkling Grades (Teoh et al. 2008)



Tilt table Testing

Subjects were placed on a tilt table and were tested for a total duration of 25 minutes with blood pressure, heart rate, and heart rhythm being monitored for the duration of the test. Initially, subjects were placed in a supine position and monitored for 10 minutes. Then, subjects were tilted to 80° for 5 minutes. Hemodynamic responses were recorded, and subjects were closely monitored in the upright position to ensure safety. Subjects were then placed in the initial supine position and monitored for 10 minutes.

Hemodynamic Measurements

Autonomic responses were monitored to ensure subject safety. Finometer® technology was used to monitor heart rate and blood pressure responses during tilt table and cold pressor testing. Heart rate rhythms were closely monitored with a 3-lead electrocardiogram.

Results

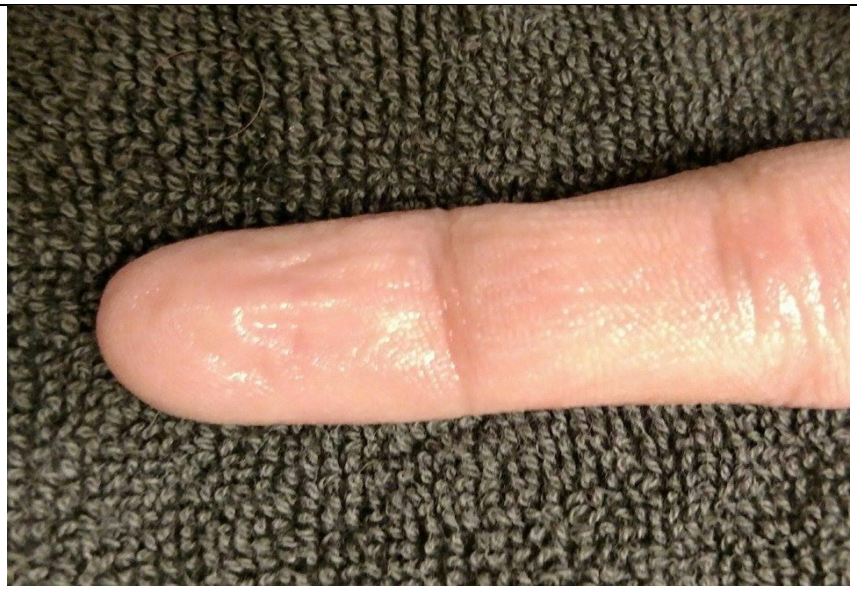
Six total subjects, three males and three females between the ages of 23 and 36, voluntarily participated in this study. Average height of subjects was 174.3 centimeters and average weight was 83.7 kilograms. The subjects were normotensive, and none were taking medications at the time of testing. The subjects were informed of the study details and all potential risks before signing an informed consent. Appalachian State University's Institutional Review Board (IRB) approved this study.

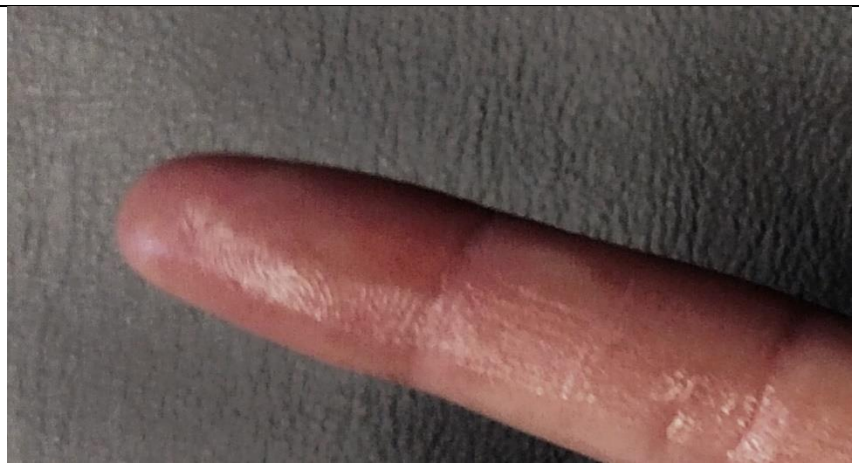
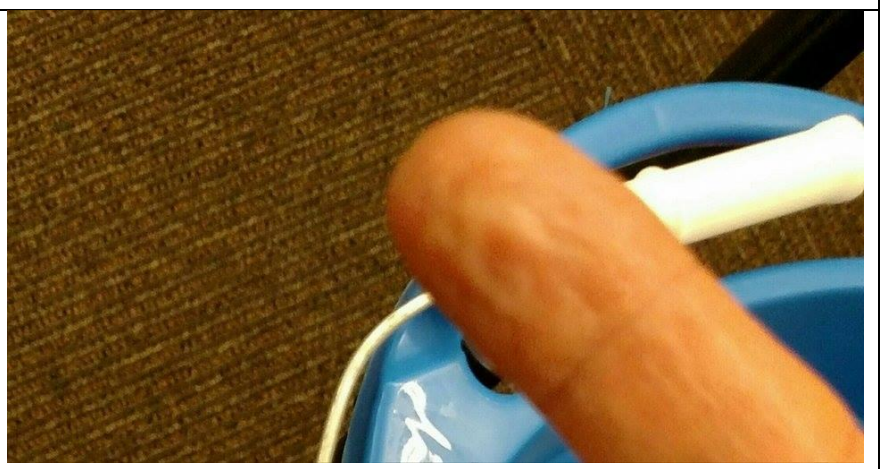
:

Supine SBP (mmHg)	Tilt SBP (mmHg)	Supine DBP (mmHg)	Tilt DBP (mmHg)	Supine HR (bpm)	Tilt HR (bpm)
119.3±7.7	130.8±8.8	66.3±3.4	83.6±9.6	57.8±10.5	75.5±12.6

Skin Wrinkling

Wrinkling was graded on a 5 point scale by Teoh et al. (2008). The results are as follows:

Subject 1 Grade 4	
Subject 2 Grade 2	

Subject 3 Grade 1	
Subject 4 Grade 2	
Subject 5 Grade 4	

Subject 6 Grade 2	

Statistical Analysis

A two-tailed t-test was used to determine significance ($p<.05$) between WISW and the low frequency to high frequency (LF/HF) ratio, a measure of HRV. Significance was not found ($t=1.48$ and $p=.18$).

Discussion

The primary aim of this study was to try to compare WISW and TTT in terms of autonomic dysfunction. TTT is a highly valuable, yet sometimes risky, way of testing autonomic function. In contrast, WISW is a test with no reported complications or adverse effects. If a correlation exists, WISW could be used in a clinical setting as a prescreening for TTT.

Heart rate variability has 3 components, very low frequency (VLF), low frequency (LF), and high frequency (HF) (Jiang et al., 2015). These components collectively are

known as total power, and the LF/HF ratio is thought to indicate sympathovagal balance (Jiang et al., 2015). The TTT is one method used to determine this ratio. These data suggest that an increase in this ratio upon tilting is associated with a higher grade of wrinkling and that a decrease upon tilting is associated with a lower grade of wrinkling. While this ratio is not fully understood, the LF/HF ratio is a component of autonomic function, and the ratio is associated with WISW (American Heart Association).

Barneveld et al. (2010) conducted a similar study using warmer water for immersion and tilting subjects to a lesser degree. This study yielded similar results, showing that a normal response to TTT was associated with a normal degree of wrinkling. All of the subjects in our study responded normally to TTT with the exception of one subject feeling light headed upon tilting. However, the subject's HR and BP rose as expected. Therefore, this was concluded to be a negative test despite showing symptoms of a positive test. No subject in our population produced an abnormal response to tilting (decrease in HR and/or BP) or wrinkling (no wrinkling), so no associations between the effectiveness of correlating WISW as a valid predictor for TTT could be made. Barneveld et al. (2010) produced 4 subjects with abnormal TTT responses and illustrated that a lesser degree of wrinkling is associated with an abnormal response to TTT with the conclusion, with further testing, WISW may be used as a precursor test to determine if TTT is needed.

A difference between this study and Barneveld et al. (2010) is the degree of tilting. Mellingsaeter et al. (2013) previously concluded that the young are more susceptible to orthostatic issues than adults. Orthostatic issues are commonly seen with postural changes. Orthostatic issues are even evaluated in a cardiac rehabilitation setting with a blood pressure test from a sitting to standing position. When going from a supine or sitting position to

standing position, the body has to respond by constricting vessels. The young are usually more active and less atherosclerotic than older counterparts (Kim & Nam, 2010). Atherosclerosis degrades the distensibility of arteries, making syncope or orthostatic issues less likely. Exercise exacerbates orthostatic issues in younger populations by dilating less atherosclerotic vessels, causing a distensible vessel to widen further (Leiria et al., 2013). Undergoing TTT prevents skeletal muscle pump forcing a rapid pressure change that causes the body to adapt quickly or faint. Generally, 60°-80° of tilting is considered optimal for determining autonomic response and keeping the subject safe. The previous study only tilted subjects to 60°, while this study tilted subjects to 80° in hopes of maximizing autonomic response. Based on tilting to the safest maximum angle, it can be concluded that all of the negative tests were true negatives.

There should be a standard process to determine degree of wrinkling (Barneveld et al., 2010). Studies range from using a visual test to using digital analysis in order to determine the amount and degree of wrinkling. Using digital analysis is sufficient for research purposes, but the process takes away from the overall application to using this test. It may be more accurate, but the type of equipment used is quite expensive. The scale provided by Teoh et al. (2008) provides an easy visual way to diagnosing wrinkling in relation to autonomic function. Digital analysis of wrinkling may have other applications in a clinical setting; but for testing autonomic function, the Teoh et al. (2008) scale proves sufficient. Barneveld et al. (2010) came to this conclusion after comparing the two tests, declaring that there is no need to use digital analysis when analyzing WISW.

Clark et al. (1984) completed a study assessing diabetics and autonomic function with different results. The study looked to correlate different types of autonomic tests and

wrinkling in diabetics. The study was not able to correlate WISW to autonomic function. Discrepancies most likely result from the population used and the determination of wrinkling.

This study confirmed that normal WISW is associated with autonomic function. Unlike previous studies, this study used a younger nonclinical population to determine if any correlations existed. The data suggests that WISW is valuable in determining autonomic function in a younger nonclinical population. Therefore, WISW may be used as a pretest for TTT.

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Vita

My name is Ricky Lee French Jr., I was born in rural western Tennessee. Growing up in a small town made me want to expand my horizons and venture out to see the world. I graduated high school and knew that my education would be my ticket out of small town USA. I attended the University of Tennessee at Martin, with the ambition of becoming a physical therapist as a biology major.

During this time of my undergraduate career, I quickly realized that I needed a more hands on approach to gain the skills needed to become a physical therapist. That is when I decided to pursue physical therapy as an exercise science major. Upon taking the remedial classes, I became captivated and in love with the field of exercise science and physiology.

I became conflicted on my career path at this time. Shadowing physical therapists proved to be monotonous and boring to me. However, I didn't know how to utilize my degree without going into rehabilitation sciences. That is when a professor of mine sat me down and really listened to me. I decided that day that I knew exactly what I wanted to do. I wanted to be him.

My senior year of undergrad was hectic. I had just decided to go to graduate school as deadlines were approaching. I applied to 3 schools and was accepted into each program. Appalachian State University was the best fit for me, and I plan to continue my education with a PhD in Clinical Physiology.