AUDREY HIX
The Relationship Between Critical Flicker Fusion Frequency and Arterial Resting Blood Pressure
(Under the Direction of BILLY R. HAMMOND JR.)

The relationship between the cardiovascular and visual systems was examined via critical flicker fusion frequency (CFF) and resting systolic blood pressure (SBP). Three different studies were conducted. Study 1 assessed and found a significant positive correlation ($p < .0002$) between resting SBP and CFF ($N = 221$). Study 2 assessed whether resting SBP and CFF covary across time for a given individual ($N = 12$). The statistical results of this study were mixed. A multiple regression analysis (using time as a factor) revealed that three participants showed highly significant covariation, six participants showed marginally significant covariation, and three participants did not show a relationship between CFF and SBP. Study 3 measured the effects of blood pressure (BP) medication on the relationship between SBP and CFF ($N = 1$). This preliminary case study indicated the possibility that BP medication could lower CFF thresholds as well as SBP.

INDEX WORDS: Critical flicker fusion frequency, Systolic blood pressure, and Flicker sensitivity

THE RELATIONSHIP BETWEEN CRITICAL FLICKER FUSION FREQUENCY AND ARTERIAL RESTING BLOOD PRESSURE

by

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CHAPTER 1: INTRODUCTION

When studying human anatomy, it is readily apparent that the functions of all the systems of the body are interrelated. For example, the body's immune system would be ineffective in combating pathogens without the aid of the circulatory system in transporting antibodies to the sites of infection. Similarly, the cardiovascular and visual systems are also interrelated. For example, response to threat, initially apprehended by the visual system (e.g. seeing an angry wolf), will cause sympathetic activation. This arousal will result in increased heart rate and elevated blood pressure.

The visual system is also influenced by the cardiovascular system. The retina, the neural tissue lining the back of the eye, has a very rich blood supply, being served by the anterior vasculature and posterior choroid. Additionally, the cortical areas of the brain responsible for vision (e.g. occipital lobe) have an extraordinarily rich blood supply. Evidence of the occipital lobe's ample supply of blood becomes strikingly apparent during conditions that affect central circulation. For example, one of the first symptoms of carbon monoxide (CO) poisoning is blurry vision. Since CO has a greater affinity for red blood cells than oxygen (O2), the fatal characteristic of CO poisoning is suffocation.

Because the retina is such a metabolically active tissue, any small reduction in blood flow will influence visual function. For example, when a vein in the eye becomes constricted or occluded (as in retinal vein occlusive disease), the visual acuity of the eye is dramatically reduced; vision becomes blurred or distorted (Cameron & Ryan, 1997). Furthermore, many blinding retinal diseases, such as proliferative diabetic retinopathy or aged-related macular degeneration (ARMD), cause circulation problems that may result in areas of the retina becoming ischemic or oxygen-deprived. As a coping mechanism, the retina will form new blood vessels (called neovascularization) in order to obtain an adequate blood supply. Unfortunately, the growth of these blood vessels damages the retina. They hemorrhage easily, which can often lead to retinal detachment, disciform scarring, and ultimately blindness. Systemic hypertension (which is the most prominent risk factor for cardiovascular disease) is the condition most commonly associated with visual diseases such as branch retinal vein occlusion, especially in people over 50 years of age (for review see Cameron & Ryan, 1997).

Diseases that affect the visual system (e.g., cataracts and ARMD) and cardiovascular system (e.g. coronary heart disease and stroke) often share similar risk factors. For example, cigarette smoking and poor diet are primary risk factors for both cardiovascular and visual diseases. Studies have indicated that cigarette smoking is strongly related to the development of cataracts and ARMD (for review see West, 1999), which are the leading causes of blindness in the world. Likewise, studies have indicated that cigarette smoking is a significant risk factor for coronary heart disease (CHD) and stroke (The Eye Disease Case-Control Study Group, 1992; Hahn, Heath, & Chang, 1998), which are two of the leading causes of death in the world. High intake of dietary fat and cholesterol is an important risk factor for both ARMD (Mares-Perlman, Brady, Klein, VandenLangenberg, Klein, & Palta, 1995) and cardiovascular disease (for reviews see Hu, Manson, & Willett, 2001; Nicolosi, Wilson, Lawton, & Handelman, 2001). This risk is largely due to intake of saturated fat rather than monounsaturated fats (Hu et al., 2001), which again is true both for visual and coronary disease.

Untreated hypertension, which I have already mentioned is a primary risk factor for cardiovascular disease (Hahn et al., 1998), is related to primary open angle glaucoma, POAG (Wilson, Hertzmark, Walker, Childs-Shaw, & Epstein, 1987). Specifically, Wilson et al. (1987) found a strong association between increased resting systolic blood pressure (SBP) and incident

POAG. This association was limited to untreated hypertensive patients. Tielsch, Katz, Sommer, Quigley, and Javitt (1995) also found a positive correlation between hypertension and POAG. However, unlike Wilson et al. (1987), these researchers expanded their analysis to include resting diastolic blood pressure (DBP) and found similar results for both SBP and DBP, particularly in older participants. Leighton and Phillips (1972) found that both SBP and DBP were greater in patients with POAG than both normal controls and patients with low-tension glaucoma.

Studies have demonstrated links between arterial hypertension and intraocular pressure (IOP) (e.g. Leske & Podgor, 1983), which is a well-established risk factor for glaucoma. Specifically, Leske and Podgor (1983) found a significant positive correlation between hypertension and IOP. Hypertension was defined as an average resting SBP of greater than or equal to 160 millimeters (mm) of mercury (Hg), which is consistent with other studies (e.g. Wilson et al., 1987), and an average resting DBP of greater than or equal to 95mmHg or a history of using anti-hypertensive medication. Although IOP is an important risk factor of glaucomatous damage to the optic nerve, it is not the defining characteristic of glaucoma. Many patients with normal IOP develop glaucoma (Litwak, 2000). Langham (1994) suggested that the diagnosis and treatment of glaucoma should be focused not only on IOP but also on the microcirculation of blood flow to discrete areas of the optic nerve via ciliary choroidal blood flow and how therapy modifies blood flow to the eyes. Langham's recommendations emphasize how even subtle variations in retinal hemodynamics can have significant influences on visual performance and disease.

The sensitivity of the eye to a flickering stimulus, or flicker sensitivity (FS), has also been shown to be significantly associated with ocular hypertension (increased IOP) and glaucoma (Tyler, 1981). Tyler (1981) found significant deficits in FS at higher frequencies of modulation, 30 to 40 Hertz (Hz), in patients with glaucoma and elevated IOP. Lower frequencies and critical flicker fusion frequency (CFF) were unaffected[1]. Tyler, Ryu, and Stamper (1984) found a significant, negative correlation between IOP and FS. Similarly, Vo Van Toi, Grounauer, and Burckhardt (1990) found that artificially increasing IOP decreases FS, the loss also being most pronounced in the highest frequency range.

The fact that FS is related to IOP and glaucoma is interesting given that hypertension is also related to IOP and glaucoma. Taken together, the results suggest that FS itself might be related to blood pressure (BP) in normal individuals. This interpretation is consistent with data from two past studies (i.e. Eisner & Samples, 2000; Hammond, Warner, & Fuld, 1995). Hammond et al. (1995) found an inverse association between acute variations in SBP and FS in 6 out of 15 participants recruited (all healthy adults). Therefore, as the participants' SBP increased, their sensitivity to flicker significantly decreased. The BP increase in the Hammond et al. (1995) study was induced by a psychological stressor. Thus, the inverse nature of the relationship may reflect dynamic changes between FS and BP. However, when the baseline data (as opposed to the change values induced by the stressor) from the "nonreactive" participants (as opposed to the "reactive" participants) are replotted against the baseline FS values, a positive correlation is observed ($r = .40$, $N = 8$). The correlation was not statistically significant, probably due to insufficient statistical power. The participants who showed "less than a 10mmHg change in SBP

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[1] Both CFF and FS measure sensitivity to a flickering stimulus; however, CFF holds the illuminance constant and varies the flickering rate of the stimulus, while FS holds the flickering rate constant and varies the illuminance of the stimulus.

from their baseline” were labeled as “nonreactive” (p. 215). Eisner and Samples (2000) found a negative correlation between mean arterial blood pressure to heart rate (MAP/HR) and FS (N = 18). MAP is the average amount of pressure needed to drive blood through the circulatory system throughout the cardiac cycle (MAP = diastolic BP + pulse pressure/ 3). Pulse pressure is the difference between SBP and DBP.

In summary, there is a vast literature connecting systemic hypertension, which is a prominent risk factor for cardiovascular disease (e.g. CHD), with visual disease such as glaucoma (Leighton & Phillips, 1972; Tielsch, et al., 1995; Wilson et al., 1987), and there are many studies connecting ocular hypertension (e.g. IOP), which is an important risk factor for glaucoma, with systemic hypertension (e.g. Leske & Podgor, 1983). In addition, many studies suggest an association between IOP and FS (e.g. Tyler, 1981; Tyler et al., 1984; Vo Van Toi et al., 1990) and systemic hypertension and FS (Eisner & Samples, 2000; Hammond et. al., 1995).

With the exception of Eisner and Samples (2000) and Hammond et al. (1995), the previously mentioned studies do not address a relationship between the normal functioning of the cardiovascular and the normal functioning of the visual system under resting conditions. Little data, beyond these two small studies, is available to adequately assess the relationship between cardiovascular and visual functioning in the absence of disease and under resting conditions. Although Eisner and Samples did assess resting blood pressure and FS in non-diseased participants, their small sample did not allow for adequate control for the important confounding influence of age. They studied individuals from 40-68 years of age. Moreover, both the Hammond et al. study and the Eisner and Samples study measured FS. FS assesses both luminance thresholds and flicker thresholds. Although under normal conditions, FS is highly related to purely temporal measures such as critical flicker thresholds (Ferry-Porter law). Older participants lose visual sensitivity (Hammond, Wooten, & Snodderly, 1998), as well as temporal resolution (Curran, Wattis, Shillingford, & Hindmarch, 1990), which complicates the interpretation of Eisner and Samples' data. In our first study (Study 1), we had a goal similar to Eisner and Samples, to quantify a relationship between visual and cardiovascular variables in healthy individuals. However, we controlled for age by only selecting participants in a young, narrow age range (~17-24). We also used a more narrowly defined visual function measure, CFF.

Critical flicker fusion frequency

Critical flicker thresholds are determined using a descending method of limits. In a typical paradigm, the flicker rate of a fused suprathreshold stimulus is reduced until a participant just perceives flicker. Critical fusion thresholds are determined by increasing the flicker rate of a flickering stimulus until the stimulus stops flickering and appears fused. CFF is taken as the average of the descending flicker value and the ascending fused value.

The fact that past studies have found that glaucoma and IOP are more related to FS than CFF (Tyler, 1981) is one indication that FS is more affected by factors influencing the eye directly. In contrast, CFF is often used as a more holistic index of visual function that is probably determined post-receptorally. For instance, Wells, Bernstein, Scott, Bennett, and Mendelson (2001) conducted a recent study showing that, for rats, CFF thresholds were determined by the simple, complex, and hypercomplex cells of areas 17 and 18 of the primary visual cortex. Furthermore, studies have found that CFF is related to improved psychomotor performance and reaction time (Grunberger, Saletu, Berner, & Stohr, 1982). Grunberger et al. (1982) also found that CFF covaried with electroencephalogram (EEG) measurements, particularly with increasing alpha activity.

Due to data such as Wells et al. and Grunberger et al., CFF is commonly used as an indicator of the overall state of arousal of the central nervous system (CNS), including variables such as mental alertness and cognitive potential (Curran, et al., 1990; Volz & Strum, 1995). In fact, CFF is widely used to study the effects of psychotropic drugs on the CNS of normal healthy participants (Smith & Misiak, 1976). Drugs that stimulate the CNS increase CFF, and drugs that depress the CNS decrease CFF (Simonson & Brozek, 1952; Smith & Misiak, 1976). Thus, if CFF is associated with higher brain arousal and SBP is associated with CFF, then an association between higher brain arousal and SBP seems highly probable.

There are many factors that affect CFF (e.g. illuminance, stimulus size, wavelength, age, smoking, diet, and disease states), which should be accounted for when using CFF as an experimental parameter. CFF increases approximately linearly with the log of illumination, which is referred to as the Ferry-Porter law. This increase in CFF is most likely related to a general speeding up of retinal processes, which occurs with increasing levels of light adaptation (Schwartz, 1999). CFF also increases linearly with the log of stimulus area; thus, flicker is easier to perceive with larger stimuli. This is referred to as the Granit-Harper law. To account for these two effects, the illumination and size of the test stimulus used in the present study were held constant.

Furthermore, age (Lachenmayr, Kojetinsky, Ostermaier, Angstwurm, Vivell, & Schaumberger, 1994; Simonson & Brozek, 1952) and smoking (Simonson & Brozek, 1952) are both negatively correlated with CFF thresholds. Age was controlled for in this study by the recruiting of a relatively young sample. Smoking status was assessed by questionnaire, and the results of the analysis are provided later in the methods section. Additionally, many cardiovascular diseases and eye diseases will reduce CFF thresholds (Curran et al., 1990;

Simonson & Brozek, 1952), and there are many drugs that raise CFF (e.g. amphetamines) or decrease CFF (e.g. barbiturates). Therefore, disease states and any drug use were also assessed via questionnaire. Due to the younger age of the sample, disease influences and influences due to prescription drug use were considered unlikely.

Systolic Resting Blood Pressure

The most common parameter utilized when assessing cardiovascular functioning is arterial resting blood pressure (RBP) because it provides a good index of cardiovascular response that is relatively easy to obtain and quantify (Sherwood & Turner, 1992). Much like CFF (Grunberger et al., 1982), SBP and DBP have been linked to ongoing electrocortical activity. Walker and Walker (1983) found that “rhythmic oscillations of the EEG were time-locked to the carotid pressure wave” (particularly those in the alpha range), and “EEG samples taken during systolic and diastolic pressure were distinctly out of phase” (p. 70-71). These results seem to suggest that cardiovascular functioning influences electro-cortical rhythms, which in turn mediate the relationship between cardiac events and behavior (Walker & Walker, 1983). The fact that the oscillations in electro-cortical activity were found primarily in the alpha range (Walker & Walker, 1983) lends support to the idea that there is a possible relationship between cardiovascular functioning and CFF, since Grunberger et al. (1982) found a positive relationship between alpha activity and CFF[2].

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[2] However, while both SBP and DBP were measured in the present study, only the results for SBP are reported. In general, we found similar results for DBP, only the effects were attenuated. Furthermore, SBP has been more heavily linked to the risk of cardiovascular diseases (e.g. heart disease & stroke) than DBP (review by He & Whelton, 1999), which lends more clinical interest to this analysis.

In addition, studies have found that SBP and DBP tend to vary with cardiac cycle during social situations and solitude, but that heart rate (HR) only shows cyclic variations during solitude (Warner & Stevens, 1991). The authors believe that their data are due to some type of feedback mechanism. Likewise, Sandman, McCanne, Kaiser, and Diamond (1977) reported enhanced visual performance during low HR suggesting that cardiac phase also influences visual perception. However, another study investigating the average differences in visual sensitivity as a function of cardiac cycles (Elliot & Graf, 1972) found small and unreliable differences.

A relatively recent study found that SBP, like CFF, might be a marker of subcortical arousal (Davies, Bennet, Barbour, Tarassenko, & Stradling, 1999). This was a clinical study that looked at a special type of sleep disorder called Cheyne-Stokes (which is a disorder of breathing during sleep). Basically, they found that the participants' SBP was in high concordance with the progression of their cortical arousal as measured by an EEG.

Purpose of Present Studies

The purpose of the present studies was to investigate the relationship between resting systemic BP and visual functioning of normotensive, healthy participants. Specifically, the cross-sectional relationship between resting SBP and CFF was assessed. Covariance between the two variables for a given participant across a temporal dimension was also evaluated. For the reasons previously outlined, we predicted that we would find a relationship between CFF and SBP. We also predicted this relationship would be positive. Past studies have suggested that SBP may be a marker of subcortical arousal (Davies et al., 1999). If higher resting SBP is arousing, and if it leads to higher brain arousal, it should also lead to higher CFF values, which covaries with CNS arousal (Wells et al., 2001). In summary, these studies attempted to address the following questions: (1.) Are CFF and resting SBP related? (2.) Is higher resting SBP arousing? (3.) Does higher resting SBP lead to higher brain arousal? (4.) Does CFF and resting SBP covary across time? (5.) What are the affects of blood pressure medication on these relationships?

In order to address these questions, three different studies were conducted. As previously alluded to, the design and motivation of the first study (Study 1) was to address the general relationship between the cardiovascular system, via SBP, and the functioning of the visual system, via CFF. Specifically, Study 1 was a between-subjects design in which participants' CFF and resting SBP were measured in one experimental session. Unlike the Eisner and Samples study (which recruited 18 middle-aged adults), a much larger sample of young adults was recruited for this study. This large sample size was necessary in order to control for the many confounds that might be expected to influence CFF and SBP. Furthermore, by utilizing a relatively younger population, variance due to the overall aging of the visual and cardiovascular systems was decreased. As previously mentioned, the visual parameter that was used was CFF as opposed to FS, and resting SBP was measured as opposed to MAP/HR, DBP, or dynamic systemic pressure.

The second study (Study 2) was a within-subjects design in which participants' CFF and resting SBP were measured on ten separate occasions. This study was designed to assess covariance in the two variables across time. The third study (Study 3) was a case study in which the effects of BP medication on the relationship between CFF and resting SBP was examined. This combination of study designs was selected in order to aid in the final interpretation of the results.

CHAPTER 2: STUDY 1

Method

Participants. Two hundred and twenty-one undergraduates (126 women and 95 men) were recruited from the University of Georgia (UGA). The mean age of participants was 19.59 years (*SD* = 2.45). Informed consent was obtained, and the Institutional Review Board (IRB) approved all experimental procedures. Participant testing and data handling was conducted according to the tenets outlined in the Declaration of Helsinki, which is a protocol accepted as a standard when testing human participants in clinical research settings.

All participants were required to fill out a brief questionnaire including personal information (e.g. age, sex, and iris color) and smoking history (e.g. current and past smoking habits). Forty-five of the participants were smokers, 31 were past smokers, and 145 had never smoked. Forty-nine had blue irises, 6 had bluish irises (e.g. blue/green, blue/hazel, and blue/yellow), 85 had brown irises, 5 had brownish irises (e.g. brown/green and brown/hazel), 36 had green irises, 2 had greenish irises (e.g. greenish-brown and greenish-hazel), and 36 had hazel irises.

The participants' Snellen acuity was also assessed. Only the right eye of each participant was measured. Ninety-one of the participants had 20/20 Snellen acuity, 5 participants had 20/17.5, and 85 had 20/15 or better visual acuity. Three participants had 20/25 Snellen acuity, 25 had 20/30, 8 had 20/40, 3 had 20/50, and one person had 20/70 visual acuity. For a summary of the data collected on smoking status, iris color, and Snellen acuity see Table 1.

Materials. An automatic, digital sphygmomanometer (Omron Healthcare, Inc., model HEM-725C) was used to measure arterial RBP, in millimeters of mercury (mm Hg), via an arm cuff on the left, brachial artery (upper arm). As previously mentioned, a Snellen eye chart was

Table 1

Smoking Status, Iris Color, and Snellen Acuity of Participants in Study 1

Variable	Number out of 221 participants	Approximate Percentages
Smoking Status		
Current smokers	45	20%
Past smoker	31	14%
Never smoked	145	66%
Iris Color		
Blue or bluish	55	25%
Brown or Brownish	90	40%
Green or Greenish	38	17%
Hazel	36	16%
Snellen Acuity		
20/15 or better	85	38%
20/17.5	5	2%
20/20	91	41%
20/25	3	1%
20/30	25	11%
20/40	8	4%
20/50	3	1%
20/70	1	0.5%

utilized to measure visual acuity. CFF was measured psychophysically in Hertz (Hz) on a Newtonian view optical system (using a 1-deg circular test stimulus). This optical system is schematicized in Wooten, Hammond, Land, and Snodderly (1999).

To avoid absorption by preretinal media (e.g. lens and macular pigment), a 570-nanometer (nm) light was used for the test stimulus. It was generated by a liquid energy display (LED) with peak energy at 570-nm (half-width =20 nm), and was not presented on a background (thus the background appeared black to the participants). Light from the LED source was collimated with planoconvex lenses. The size of the test stimulus was defined by a circular aperture placed after the collimating lenses of the system. The stimulus was delivered in square wave alteration, and the rate at which it was presented could be varied over a 1-50 Hz range. The illuminance of the 570-nm light was set at 30 candelas per square meter, and the radiance was 0.34 nanowatts. The system was calibrated periodically to assure that these settings remained stable. The entire optical system was encased in a black, rectangular Plexiglas box. A 1-inch, circular hole in the front of the box allowed participants to view the stimulus. A chin and forehead rest was utilized in order to minimize head movements and maintain the visual angle of the test stimulus.

Design and procedure. A between-subjects design was employed in Study 1, and each session lasted approximately 30 minutes. Before any measurements were taken, the participants filled out the consent form and questionnaire. Then, the participants' Snellen acuity was assessed by the experimenter and recorded on the questionnaire. Next, the participants' RBP was measured on their left brachial arteries (pulse was recorded along with RBP). After obtaining RBP, the experimenter measured the participants' CFF. At the end of the experimental session, in order to obtain average measurements, the participants' RBP and CFF were measured a second time.

CFF was assessed using the ascending and descending Method of Limits. First, the participants were placed in a darkened room (one at a time) and instructed to rest their heads on a headrest in front of the Newtonian view optical system. Then, the flickering rate of the 1-deg, 570-nm circular stimulus was set at 12 Hz (consistent with past studies, Curran et al., 1990), and participants' were asked if they could see a black background with a green flickering circle. Upon receiving an affirmation from the participants, the experimenter instructed them to state when the flickering appeared to stop. Then, the experimenter gradually began increasing the flicker rate of the stimulus until the participant perceived the stimulus as fused (the flickering stopped); this rate (in Hz) was recorded. Finally, the experimenter adjusted the flickering rate well above the previously obtained rate and instructed the participants to state when they first perceived the stimulus to start flickering. This number was also recorded. The experimenter then averaged the ascending and descending values to obtain one CFF measurement.

Results

The overall average resting SBP was 115.73 (*SD* = 14.41), and the overall average CFF threshold for the participants was 23.12 (*SD* = 2.73). To assess whether there were any sex differences, we conducted two One-Sample T-Tests (in SPSS 10.1) comparing the male and female SBP and CFF thresholds. The results of these tests indicated that there was a statistically significant difference between the average resting SBP measurements for the males (*M* = 125.19, *SD* = 12.40) and females (*M* = 108.59, *SD* = 11.42), *t* = 10.193 ($p < 0.0001$). Moreover, the results indicated that there was a statistically significant difference between the average CFF thresholds for the males (*M*= 23.87, *SD* = 2.87) and females (*M* = 22.54, *SD* = 2.48), $t = 3.61$ ($p < 0.0001$).

We also did a correlational analysis (Pearson's *r*) between SBP and CFF. This analysis revealed a statistically significant, positive correlation ($r = 0.23$, $p < 0.0002$) between CFF and resting systolic BP (see Figure 1). We did not find a sex difference in the SBP-CFF relationship.

Discussion

The results of Study 1 support the hypothesis that resting SBP and CFF are positively correlated. Additionally, the results reveal a statistically significant sex difference between both SBP measurements and CFF thresholds. In particular, the males had higher resting SBP and higher CFF thresholds. Note that the direction of this result is consistent with the hypothesis that SBP and CFF are positively correlated. These sex differences may be clinically meaningful given the fact that males have such higher incidence of cardiovascular disease. The average SBP of the males was higher than the females despite the relatively young age of this sample. The results would imply that even young males might have higher levels of brain arousal compared to females. This higher state of arousal may be linked to increased SBP. If high levels of arousal is rewarding, increased blood pressure in the males may actually be "learned" through operant mechanisms (see Dworkin, Filewich, Miller, & Craigmyle, 1979).

Furthermore, the sex difference found in this study is consistent with past research. For example, it has been noted that in nearly all developed countries (e.g. North American, Europe, and Japan) young adult women consistently demonstrate lower systolic and diastolic pressures than men (Whelton, He, & Klag, 1994). However, this association is variable over the entire lifespan. The BP of children does not show any statistical effects of sex (for review see Laragh & Brenner, 1995); however, in adolescence (e.g. starting around age 13) the mean SBP of boys is significantly higher than that of teenage girls (Baron, Freyer, & Fixler, 1986). Furthermore, between the ages of 35 - 44 years, SBP remains higher for men. However, by middle age (55-64 years) the difference becomes much smaller, and then by the sixth and seventh decades, women have slightly higher SBP than men (OPCS, 1994).

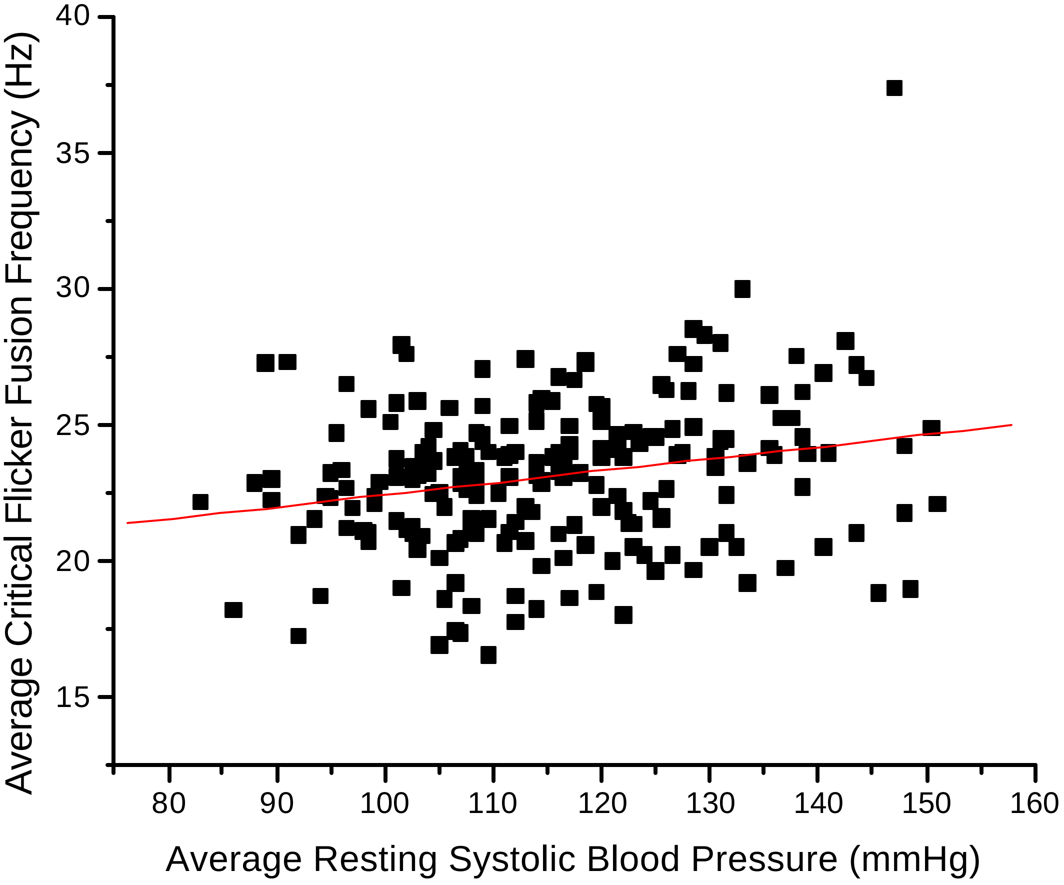

Figure 1. The relationship between CFF and SBP ($Y = 18 + 0.04x$, $r = 0.23$, $p < 0.0002$) for the entire sample tested ($N = 221$).

CHAPTER 3: STUDY 2

Method

Participants. A sample of 12 graduate and undergraduate students (3 men and 9 women, mean age = 24.42, *SD* = 6.33) were recruited from the University of Georgia student body. Informed consent was obtained, and the IRB approved all experimental procedures. Consistent with Study 1, participants were required to fill out a questionnaire to assess their personal data (e.g. age, sex, and iris color) and smoking history (e.g. current and past smoking habits). Likewise, the visual acuity of their right eyes was measured by the experimenters using the Snellen eye chart.

Because Study 2 recruited a much smaller sample size than Study 1, more visual, medical, and dietary information was considered from the participants' questionnaires. Refractive errors, eye surgeries or treatments, history of eye disease, any medical conditions or medications, and whether or not each participant was a vegetarian was assessed. All of this information is listed in Tables 2.1 and 2.2.

Materials. All materials used in Study 2 were identical to those used in Study 1. Average resting BP was assessed with an automatic sphygmomanometer, visual acuity was measured with a Snellen eye chart, and average CFF was measured on the Newtonian view optical system (using a 1-deg circular test stimulus). Again, only the right eye of each participant was measured.

Design and procedure. A within-subjects design was employed for Study 2. The participants' SBP and CFF were measured in the exact same manner as listed above; however, measurements were taken on ten separate occasions. These separate days were not equally spaced. Because of time constraints, three of the participants were unable to complete all ten sessions. Participants MNK and KLM completed 9 sessions, and GLS completed 8 sessions.

Table 2.1

Qualitative Information on Study 2 Participants

Variable	Number out of 12 participants	Participant Initials
Smoking Status		
Current	7	HST, JFC, KAM, KLM, MNK, MJP, & SRP
Past	1	GLS
Never	4	DDW, DLG, GIC, & JRD
Iris Color		
Blue	3	GIC, JFC, & JRD
Bluish (blue/gray & blue/green)	2	GLS & KAM
Brown or Brownish (e.g. brown/hazel)	5	DDW, DLG, KLM, MNK, & MJP
Gray or Grayish (e.g. gray/green)	2	HST & SRP
Snellen Acuity (right eye only)		
20/15 or better	4	DLG, JFC, KLM, MJP, & SRP
20/17.5	2	HST & KAM
20/20	3	DDW, GIC, & JRD
20/30	1	MNK
Not reported	2	GLS

Table 2.2

Qualitative Information on Study 2 Participants continued…

Variable	Number out of 12 participants	Participant Initials
Current Eye Diseases or Conditions		
Refractive Errors	9	DDW, GLS, JRD, KAM, KLM, MNK, MJP, SRP, &
Anomalous Trichromat	1	GIC
Past Eye Diseases, Conditions, or Surgeries		
Conjunctivitis	1	SRP
Lasik surgery	1	GIC
Family History of Eye Disease		
Cataracts	7	GLS, HST, JRD, KAM, KLM, MNK, & MJP
Glaucoma	1	KLM
ARMD	1	GLS
Medical Conditions & Medications		
Asthma (Singulair)	1	KAM
Birth Control	2	KLM & SRP
Anti-depressants (Serzone & Zoloft)	2	KAM & SRP
Diet Information		
Vegetarian	1	SRP

Results

Analysis one. To assess any covariance between the two variables (CFF and resting SBP), the data of each participant was examined separately. Each person's data was plotted on a double-Y line graph. Time (specified in days) was placed on the abscissa, and average resting SBP and average CFF was placed on the two ordinates. This allowed us to visually assess any obvious covariance between the two variables. From this initial examination, we identified 5 out of the 12 participants that illustrated potential significant covariance (see Figures 2 - 6).

Analysis two. An unlagged cross-correlation function was employed (via the statistical program SPSS 10.1) for each participant (averaging the two measures taken during a given session). With critical values of $r = 0.55$ ($df = 8$, $p < 0.05$) and $r = 0.62$ ($df = 6$, $p < 0.05$) , this analysis yielded marginally significant results for two participants, GLS and JRD ($r = -0.52$ and $r = -0.41$ respectively). The analysis revealed null results for all subsequent participants. In addition, we conducted an unlagged cross-correlation function <u>on all the data points</u> collected for each individual. For instance, instead of just analyzing the 10 average CFF and SBP measurements for participant JFC, we analyzed all 20 CFF and SBP measurements obtained from this individual. This analysis yielded marginally significant results for three participants, DLG, JRD, and MJP (r = 0.30, r = -0.37, and r = -0.35 respectively), and significant results for one participant, JFC. JFC's results revealed a statistically significant positive unlagged cross-correlation ($r = 0.40$, $p < 0.05$).

Analysis three. Our preliminary data analysis (see Figures 2 - 6) suggested that, while there appeared to be significant covariation for many days during the study period, some days were markedly divergent. Therefore, we conducted the analysis again but removed the data for the one day that seemed most divergent. Participants DLG, GIC, JFC, JRD, and KAM all showed statistically significant cross-correlations, which is for the most part consistent with our initial beliefs that there was significant covariance between the CFF thresholds and SBP measurements of these particular participants. For more detailed information see Table 3. This analysis suggests that with additional measurements the results may have reached significance without the necessity of windzoring the data.

Table 3

Results of the unlagged cross-correlation analysis on the windzored, Study 2 data.

Participant	Removed data Points	Cross-correlation	significance level (one-tailed)
DDW	Day 7	-0.18	Not significant
DLG	Day 1	0.44*	0.05
GIC	Day 9	0.46*	0.025
GLS	Day 1	-0.18	Not significant
HST	Day 2	0.07	Not significant
JFC	Day 7	0.55*	0.01
JRD	Day 3	-0.39*	0.05
KAM	Day 8	0.50*	0.025
KLM	Day 1	-0.03	Not significant
MNK	Day 5	-0.09	Not significant
MJP	Day 2	-0.22	Not significant
SRP	Day 2	-0.06	Not significant

* = significant

Analysis four. The pattern of covariance and non-covariance on the double-Y line graphs constructed from the data, revealed that for some of the participants the two variables covaried on days 1-5 but then fell out of sync on the last days of the study (see Figures 2 - 4, & 6). JRD's graph exhibited the exact opposite pattern (see Figure 5). Therefore, we conducted a multiple regression analysis (in the statistical program Origin 6.0) in which we regressed CFF on SBP and

Trial (coded as early trials and late trials). For instance, the measurements taken in trials 1-10 (from days 1-5) were coded as 1’s and trials 11-20 (from days 6-10) were coded as 2’s. This analysis yielded statistically significant *F*-values for 3 out of 12 participants (DDW, JRD, and KLM), 7 participants showed marginally significant results (DLG, GLS, HST, JFC, KAM, MNK, and SRP), and the remaining 2 participants (GIC and MJP) did not yield statistically significant results (see Table 4).

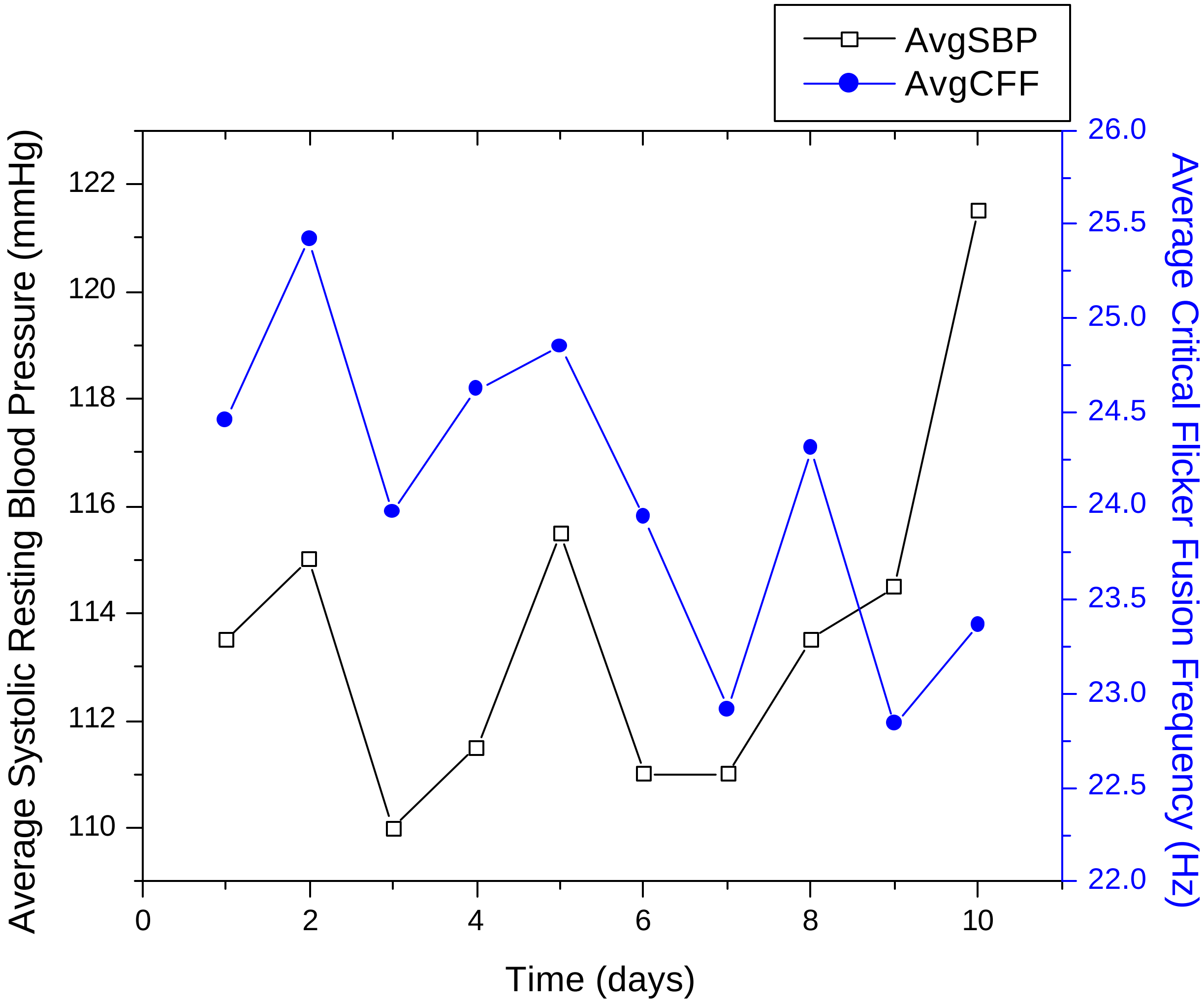

Figure 2. Data from participant DDW.

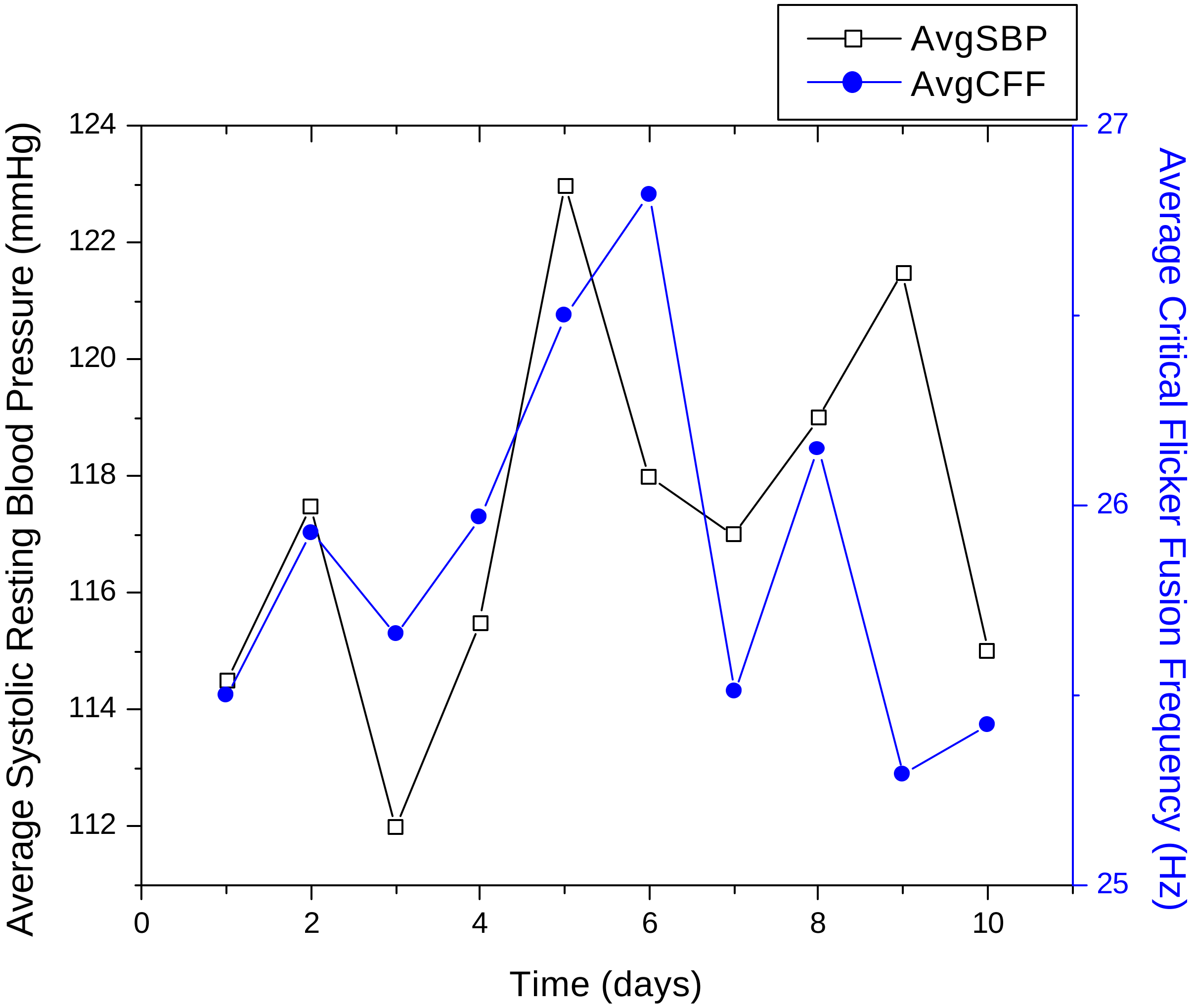

Figure 3. Data from participant GIC.

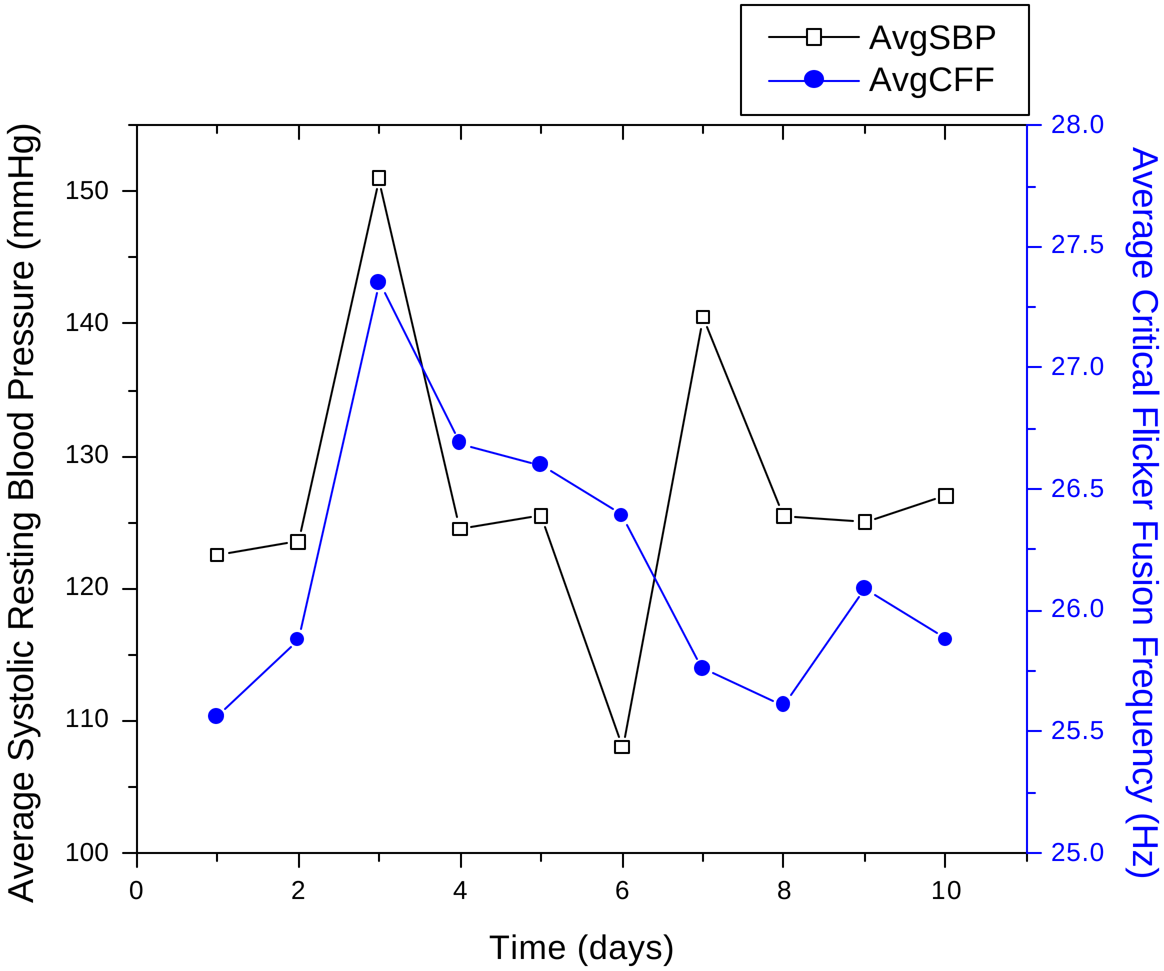

Figure 4. Data from participant JFC.

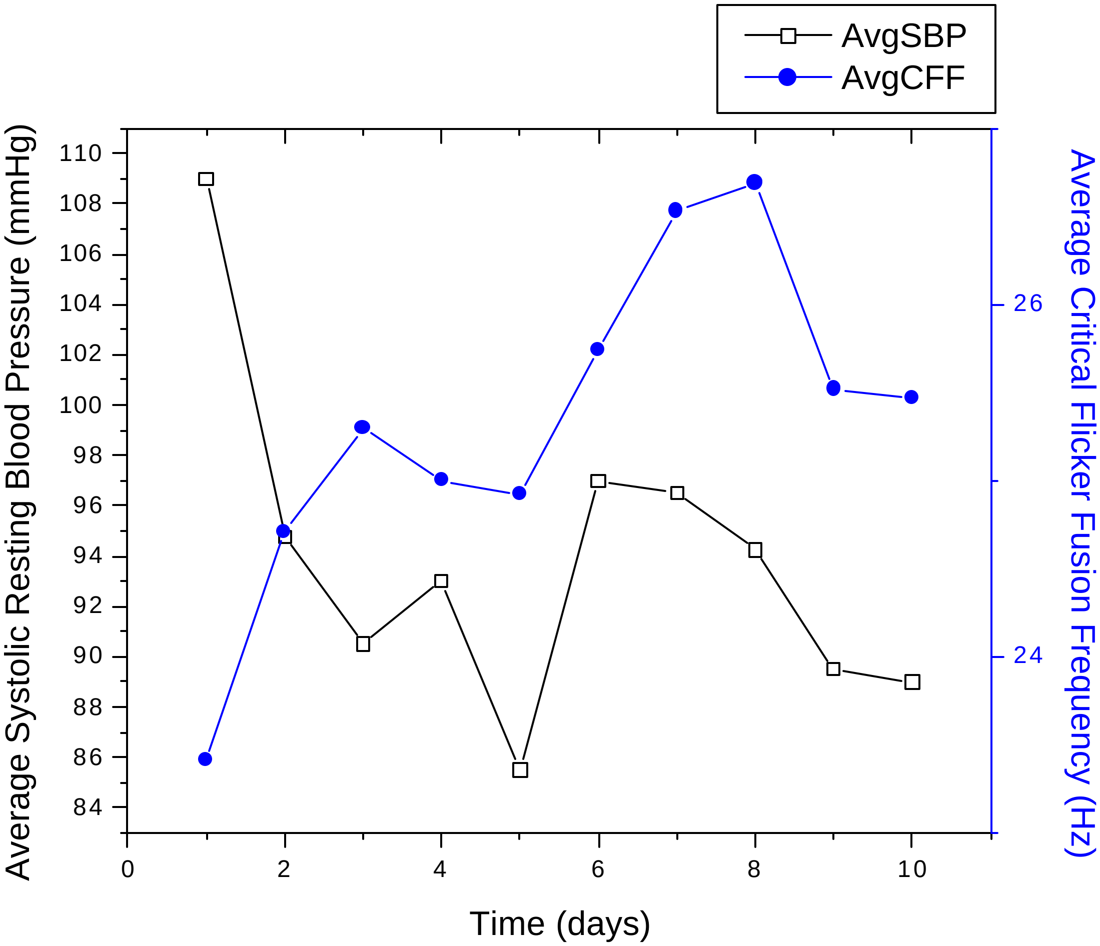

Figure 5. Data from participant JRD.

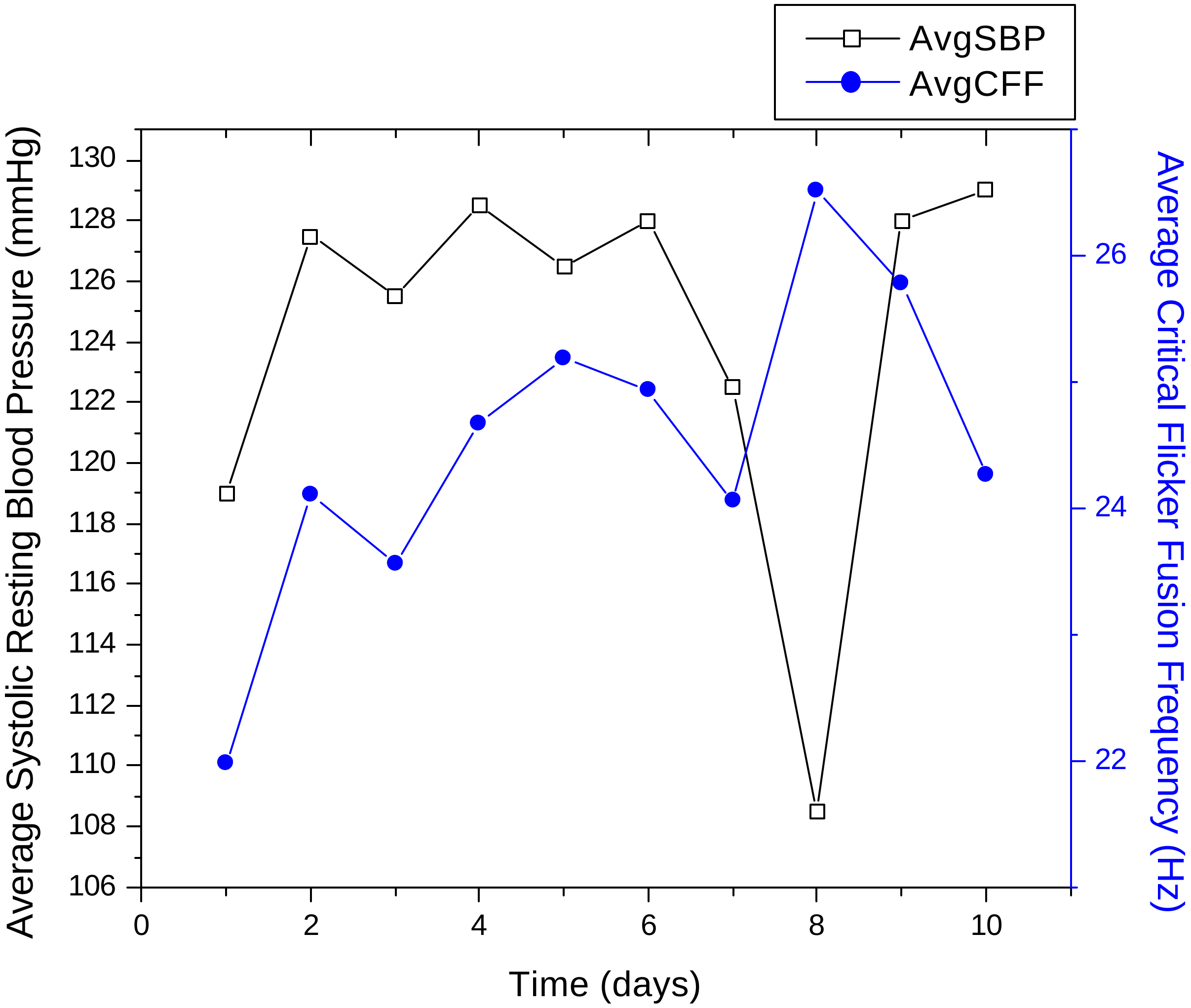

Figure 6. Data from participant KAM.

Table 4

Results from the Multiple Regression Analysis Study 2 Participants

Participant	R-squared	F-statistic	P-value of F-statistic
DDW	0.50*	8.51	0.003
DLG	0.23	2.61	0.10
GIC	0.08	0.77	0.48
GLS	0.28	2.54	0.12
HST	0.21	2.29	0.13
JFC	0.26	2.91	0.08
JRD	0.60*	12.77	0.0004
KAM	0.25	2.86	0.08
KLM	0.37	4.32	0.03
MNK	0.26	2.56	0.11
MJP	0.13	1.28	0.30
SRP	0.22	2.45	0.12

* = $p > 0.025$

Discussion

The results of Study 2 are mixed. The cross-correlation analysis (analysis two) seemed to support the null hypothesis that CFF and resting BP do not vary together across time. However, Figures 2-6 suggest more than just random fluctuation. When we removed the data from one day for each individual (analysis three), the results showed statistically significant results for 5 out of the 12 participants. This suggests that we had insufficient statistical power to adequately determine the magnitude of this effect. Indeed, two out of the three participants for whom we obtained "marginally" significant results for in the analysis of the raw data were two of the participants that did not complete the entire ten sessions of the study (MNK and GLS).

An examination of Figure 2- 6 (analysis one) suggest the possibility of a confounding variable, which is sometimes present and sometimes absent. One possibility is based on the results of Hammond et al. (1995). Their study suggested that, although resting BP may be positively correlated with CFF, dynamic changes in BP are inversely correlated with CFF. It should be noted here that this change is bi-directional. Increasing BP leads to decreasing CFF, and decreasing BP leads to increasing CFF. It is possible that on days where BP and CFF appeared divergent, the participants BP may not be reflecting true resting levels. Therefore, one aim of future studies could be to analyze this possibility by carefully obtaining measures of SBP that represent true resting levels.

CHAPTER 4: STUDY 3

Method

Participants. Study 3 consisted of one, white male, 36 years of age. The participant (BRH) had never smoked, had green/hazel irises, had a Snellen acuity of 20/20 in his right eye, and had myopia (for which he wore corrective eye glasses). In addition, he had no history of eye diseases, and he was a vegetarian.

Materials. All materials used in Study 3 were identical to those used in Study 1 except for one. Arterial resting BP was assessed with an automatic sphygmomanometer, visual acuity was measured with a Snellen eye chart, and average CFF was assessed by the Newtonian view optical system (using a 1-deg circular test stimulus). Consistent with Study 1 and 2, only the right eye of the participant was measured. In addition to these materials, a generic brand of the drug Ramipril, Altace, was prescribed by a doctor and taken by the participant for the second half of the study (days 7-12). The participant took approximately 2 milligrams (mg) of the drug a day for 15 days.

Design and procedure. The participant's CFF and SBP were assessed in the above-mentioned manner (see Study 1) on six different days prior to any medication. These data provided a solid baseline measurement. Then, the participant began taking the Altace. Two days later (allowing time for the drug to take affect), the participant's CFF and SBP were measured again and on five other subsequent days.

Results

Data for this participant is presented in Figure 7. Note that the data are partitioned into pre-medication and post-medication trials. His average SBP was 126.67 (*SD* = 10.71), and his

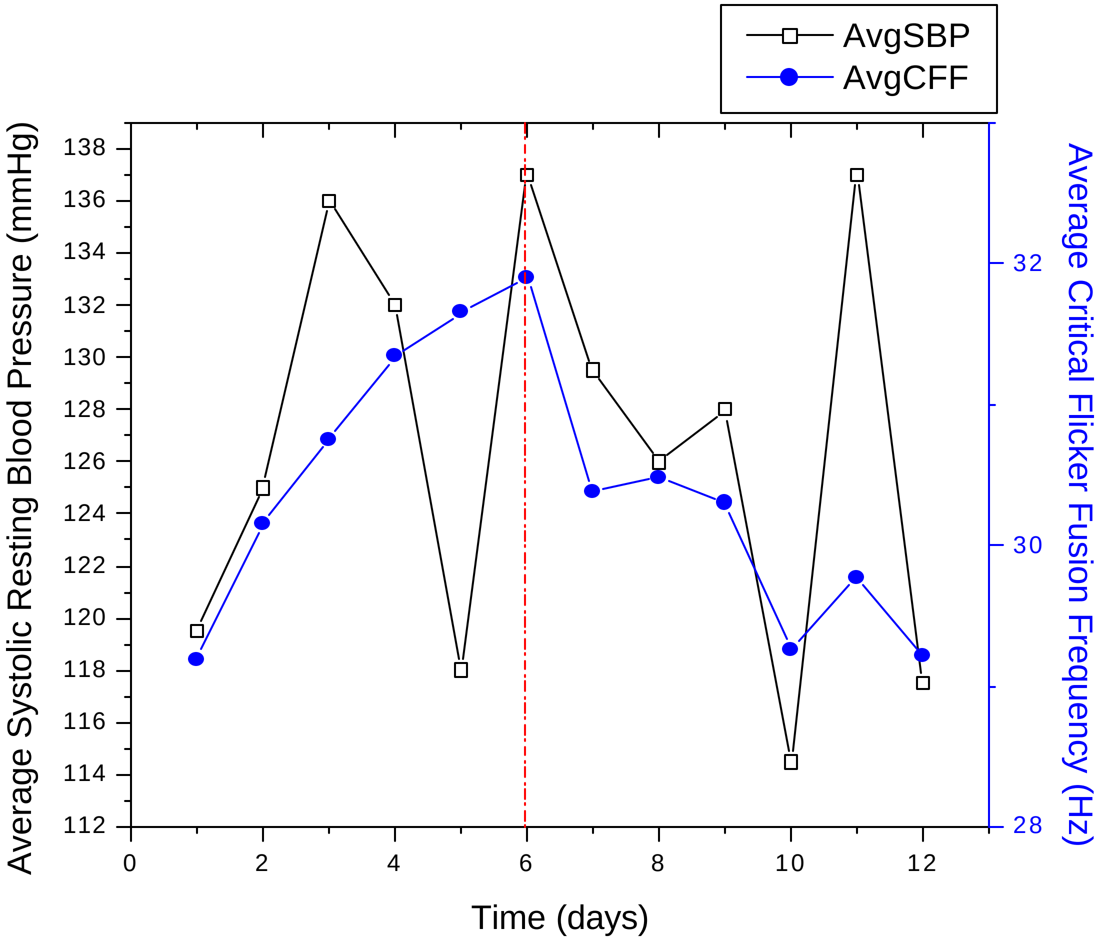

Figure 7. Data for participant BRH (pre-medication and post-medication measurements are partitioned by the dotted line down the center of the graph).

average CFF threshold was 30.36 (*SD* = 0.94). Both of these levels are higher than average, which is consistent with the results of Study 1. BRH's average pre-medication SBP was 127.92 (*SD* = 11.90), and his average post-medication SBP was 125.42 (*SD* = 9.74). BRH's mean pre-medication CFF threshold was 30.83 (*SD* = 0.99), and his post-medication CFF threshold was 29.90 (*SD* = 0.61).

Since we were interested in whether or not BP medication decreases CFF thresholds as well as resting SBP, we conducted two Paired Samples T-Tests (in SPSS 10.1) on the pre-medication (trials 1-12, taken on days 1-6) and post-medication measurements (trials 13-24, taken on days 7-12). One was conducted on the pre- and post-medication measurements of resting SBP, and the other was conducted on the CFF assessments. The purpose of these analyses was to determine if the pre-medication measurements were statistically significant from the post-medication measurements. Interestingly, the findings of the one-tailed T-Test on SBP were not significant ($t = 0.52$, $p < 0.31$), which indicated that the BP medication did not decrease the participant's BP as intended. However, the results of the one-tailed T-Test on CFF were significant ($t = 2.15$, $p < 0.03$), which indicated that the BP medication did decrease BRH's CFF threshold.

Furthermore, the data were analyzed using an unlagged cross-correlation function and a multiple regression analysis in which CFF was regressed on resting SBP and trial (coded as before and after intervention). Since BRH's CFF and SBP was measured on 12 separate days, both analyses consisted of 24 trials (instead of 20 trials as used in Study 2), which added considerably more statistical power to the results.

The results of the cross-correlation analysis (using a one-tailed alpha level) revealed a statistically significant correlation coefficient ($r = 0.42$, $p < 0.025$). Similarly, the findings of the multiple regression analysis revealed a statistically significant F statistic ($F = 6.61$, $p < 0.006$) and r-value ($r = 0.39$, $p < 0.05$). The regression equation for the best fitting line between CFF, SBP, and trial (for BRH's data) was Y = 27.63 + 0.03x (SBP)+ -0.85x (trial).

Discussion

The findings of Study 3 support three of the initial hypotheses (1) that CFF and resting SBP are positively correlated (2) that CFF and resting SBP vary together across time, and (3) that CFF would decrease with resting SBP when taking blood pressure medication. Specifically, the significant cross-correlation function strongly suggested a covariance of resting SBP and CFF over time. In addition, the multiple regression analysis indicated that the participant's CFF threshold could be predicted by resting SBP and trial (coded as pre- and post-medication). Finally, the results of the Paired Samples T-Test suggested that BP medication influenced this participant's CFF thresholds.

In summary, the relationship between resting SBP and CFF for this participant were quite robust. Preliminary results motivates the need to study more participants in order to clarify these effects. Although not statistically significant, it is likely that BRH's BP was also affected by the medication. Unlike his CFF values, however, which only ranged over about 3 Hz (~10% of total), his BP was quite variable (ranging from 114 to 137; ~18% of total). The greater variance reduces the statistical discriminability of the test.

CHAPTER 5: GENERAL DISCUSSION

The combination of results from the present three studies strongly suggest that CFF and resting SBP are related. This result is consistent with past studies that found a relationship between cardiovascular and visual functioning in normal, healthy adults (e.g. Eisner & Samples, 2000). A statistically significant sex difference was also found in Study 1. The males had higher resting SBP and higher CFF thresholds. Importantly, the results suggest that normal variations in the BP of even young individuals can have measurable impacts on vision. This relationship may reflect an important link in the development of long-term essential hypertension and cardiovascular disease. This implication would be consistent with the biofeedback model developed by B. R. Dworkin (for review see Dworkin, 1988).

Dworkin developed a model that attempts to explain the etiology of essential hypertension. He outlined how physiological reactions to stressful events can lead to essential hypertension through chronic baroreceptor activation. Based on his theory, the baroreceptor reinforcement hypothesis, hypertension can be learned through operant mechanisms. Baroreceptors are receptors that signal the stretching of major arteries such as the carotid and aorta. Increased activity of the baroreceptors results in a signal being sent to the medulla, which activates the vagal center causing reduction of BP. Thus, the baroreceptor-medulla-vagus reflex arc forms a negative feedback loop which helps maintain homeostasis within the circulatory system. Dworkin reviews evidence that showed that activation of the baroreceptors had the secondary effect of dearousing the brain (through inhibition of the ascending reticular system). This effect, he argued, was positively reinforcing since acute arousal is generally aversive. Since the ultimate effect of having a BP response to a stressful situation is rewarding, the probability that one would have such responses is increased. Having more BP reactions to stressful situations over time would lead to chronic hypertension.

Many studies have examined how BP can be operantly conditioned (Elbert, Roberts, Lutzenberger, & Birbaumer, 1992; Pickering, Brucker, Frankel, Mathias, Dworkin, & Miller, 1976; Plumlee, 1969). For instance, Plumlee (1969) conducted a study on four rhesus monkeys in which he demonstrates the ease with which large BP rises can be conditioned. In addition, at least one study has indicated that chronic high BP can be conditioned (Jonsson & Hansson, 1977). Consistent with Plumlee (1969), Elbert et al. (1992) found that participants were successful (through the biofeedback mechanism mentioned previously) at learning to control their BP, albeit for monetary reward. Furthermore, this study assessed whether instrumentally-learned BP responses have any effects on electrocortical activity. Their study examined whether baroreceptors regulate the cardiovascular system by the use of cortical inhibition as proposed by Dworkin (Elbert et al., 1992). They found, through EEG and electrocardiogram (ECG) measurements, a temporal relationship between cardiovascular and electrocortical changes which supported their conclusion that “differentiation of slow potentials was secondary to activation of the baroreceptors” (Elbert et al., 1992, p. 161). They also state that the positive-going slow potentials they found signify cortical inhibition.

Hammond et al. (1995) looked at dynamic changes in BP rather than normal variations in resting BP. Consistent with Dworkin (1988), they found that acute elevations in BP inhibit sensory systems, specifically FS thresholds. Thus, as BP increases, FS decreases. This pattern of results is consistent with research conducted on other sensory thresholds (e.g. pain). For example, Angrilli, Mini, Mucha, and Rau (1997) conducted a study investigating the relationship between pain thresholds and BP. Particularly, this study evaluated whether participants, who were experiencing painful stimulations, preferred one of two conditions, baroreceptor activation or baroreceptor inhibition. The authors recruited normotensives and hypotensives as participants, and used the PRES (cardiac phase-related external suction) technique to induce pain. This technique involved placing a cuff on the neck at the carotid artery. Electrical pulses were delivered either during systolic suction (the largest baroreceptor activation) or diastolic pressure (the largest baroreceptor deactivation). The results of the study indicated a negative correlation between DBP (baroreceptor deactivation) and sensory thresholds (r = -0.44), and a positive correlation between SBP (baroreceptor activation) and pain thresholds (r = 0.27). Painful stimuli were perceived as less painful when presented during baroreceptor activation in the Normal BP group. However, there was no significant difference in the Low BP group. Therefore, the data indicate that participants with normal to high BP exhibit baroreceptor modulation of pain responses; however, participants with low BP do not. The results of this study are consistent with a past research (e.g. Rau, Brody, Larbig, Pauli, Voheringer, Harsh, Kroling, & Birbaumer, 1994). One significant confound in this study (which is pretty common with research on pain thresholds) was that all of the participants were men. In addition, studies have shown that normotensive individuals with a parental history of hypertension (thus at high risk for developing hypertension) had significantly higher pain thresholds than participants of normotensive parents (Page & France, 1997).

In contrast, the present studies indicate that normal variations in <u>resting</u> BP actually increase sensory thresholds and cortical arousal rather than inhibit them (e.g. as BP increases, CFF thresholds increases). Taken together, the results of the above mentioned studies suggest the existence of two different mechanisms of reward, short-term de-arousal and long-term arousal.

Study 2 of this paper attempted to address any covariance between resting SBP and CFF over time, which would have lent additional support to the previous postulation that the two variables have a long-term association and impact on one another over time. However, the results of this study are mixed. Statistically only a few of the results from this study support the hypothesis that CFF and resting SBP vary together across time. Most of the data seemed to indicate that the two variables are not correlated and randomly fluctuate. Overall the statistical analyses of Study 2 indicated a weak and unreliable association. However, when we removed the data from one particularly divergent day for each individual, the results convey statistically significant results for 5 out of the 12 participants. Thus, these results suggest that with additional measurements the results would have been statistically significant without the necessity of windzoring the data. Furthermore, it was postulated that the days in which SBP and CFF seem to vary together (as seen in Figures 2-6) are due to true resting SBP; however, the days in which SBP and CFF fluctuate randomly are due to acute changes in SBP.

Study 3 was a case study that assessed the effects of BP medication on CFF thresholds. Although, the actual statistical analyses of the data collected for Study 3 conveyed a strong cross-correlation of resting SBP and CFF and a definite influence of BP medication on CFF thresholds, there was only one participant. Thus, even though the data lend some support to all three hypotheses (that resting SBP and CFF are positively correlated, that resting SBP and CFF vary together across time, and the BP medication affects CFF thresholds), the data from one case study is insufficient in order to generalize to the larger population.

In conclusion, the leading cause of death in the western world is cardiovascular disease. Moreover, approximately 38 million people are blind, and a further 110 million have low vision and are at risk for blindness in the world (Thylefors, Negrel, Pararajasegaram, & Dadzie, 1995).

Thus, empirical evidence for a quantifiable relationship between these two systems could potentially have implications for the medical and scientific communities. One possible application of the present studies could be the use of CFF as a possible biomarker for the future development of hypertension. The finding that there is an association between SBP and CFF is consistent with the idea that elevated resting BP is related to increased central arousal. If increases in central arousal over time are rewarding, then efforts to block this arousal may reduce the probability of developing chronic high BP. The fact that the CFF of the participant in Study 3 lowered significantly in response to BP medication is consistent with this possibility.

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