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Power Spectral Components of Heart Rate Variability at Rest and Exercise After Surgical Repair of Tetralogy of Fallot.

A thesis submitted to the
Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the Degree of Master of Arts.

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PART TWO: EXPERIMENTAL STUDY

Power Spectral Components of Heart Rate Variability at Rest and Exercise After Surgical Repair of Tetralogy of Fallot.

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Experimental Study

LIST OF ABBREVIATIONS

CR = controlled respiration

DBP = diastolic blood pressure

ECG = electrocardiogram, electrocardiographic

HF = high frequency

HUT = head-up tilt

HRV = heart rate variability

LF = low frequency

nu = normalized units

SBP = systolic blood pressure

TOF = tetralogy of Fallot

VLF = very low frequency

ABSTRACT

An abnormal chronotropic response to exercise is a common finding following surgical repair of tetralogy of Fallot (TOF) which has generally been attributed to a putative sympathetic dysfunction. There exists little information on sympathetic function in patients operated for a congenital heart defect to support such a claim. This study used spectral analysis of heart rate (HRV) and blood pressure (BPV) variability to examine sympathovagal influences on the sinus node in 9 adolescents operated for TOF 13.0 ± 1.12 years previously and in 8 healthy age and sex-matched control (CTRL) subjects. Continuous ECG and BP recordings were obtained under supine or seated resting positions, with or without controlled respiration at 0.20 Hz (CR); after passive 85° head-up tilt (HUT); during cycling at steady-state heart rates of 100 and 120 bpm (Ex 100, Ex 120), and after 10 and 20 minutes of passive seated recovery. When compared to age-matched control subjects results showed total R-R variance to be lower in 7 of 8 patients for all non-exercising conditions and the mean values to be lower during CR ($p < 0.05$) (TOF: 2662.9 ± 765.41 vs. CTRL: 6803.1 ± 1453.03, ms^2). HUT resulted in a significant increase in the diastolic blood pressure (DBP) LF component in TOF which was also associated with a rise in DBP in patients but not in CTRL. Total R-R variance (ms^2) during exercise was significantly reduced from baseline yet was similar in both groups (Ex 120: TOF: 572.8 ± 105.34 vs. CTRL: 503.9 ± 100.95). Spectral component analysis showed similar HF and LF components in both groups at Ex 100 while a further relative decrease in HF and inversely an increase in the LF component was observed at Ex 120 in TOF but not in CTRL ($p < 0.05$) (Ex 120: LF/HF: TOF: +120.7 ± 44.86 vs. CTRL: -21.8 ± 10.86, %). This could not be explained by differences in respiratory

frequencies which were not different between groups under any condition. The observed chronotropic limitation during HUT in addition to the higher LF R-R component observed during Ex 120 may be taken to reflect disturbances in sympathovagal balance in TOF exhibiting excellent post-surgical clinical status.

RÉSUMÉ

Une limitation chronotrope à l'exercice maximal a été communément rapportée chez les patients opérés avec succès pour une tétralogie de Fallot (TOF). Ceci est généralement attribué à une dysfonction du système nerveux autonome bien qu'il n'existe actuellement aucune information précise sur la fonction sympathovagale des personnes opérés pour une TOF. L'objectif de ce travail était de comparer les influences vagale, sympathique ou le rapport sympathovagal (LF/HF) dans la variabilité de la fréquence cardiaque et de la pression artérielle déterminée par analyse spectrale chez 9 TOF et 8 témoins (CTRL) en santé pairés pour l'âge et le sexe . L'ECG et un enregistrement de pression continu au doigt (FINAPRES) ont été obtenus en position allongée ou assise au repos lors d'une respiration spontanée ou d'une fréquence respiratoire imposée à 0.20 Hz (CR); après épreuve d'orthostation verticale passive à 85°(HUT); au cours d'un effort sur cycloergomètre à des fréquences cardiaques stables de 100 et de 120 bpm (Ex 100, Ex 120), respectivement ainsi qu'après 10 et 20 minutes de récupération passive. Les résultats indiquent une variance R-R totale plus faible que les CTRL chez 7 des 8 patients pour toutes les conditions expérimentales sauf l'effort. La variance moyenne du R-R observée en situation de CR visant à minimiser sa dispersion, était significativement réduite ($p < 0.05$) chez les TOF (TOF: 2662.9 ± 765.41 vs. CTRL: 6803.1 ± 1453.03, ms^2). Une augmentation de la variabilité LF de la pression artérielle diastolique associée à une élévation de cette pression était observée en réponse à HUT chez les TOF mais non chez les CTRL. La variance totale de R-R (ms^2) était significativement réduite au cours de l'effort dans les 2 groupes par rapport au repos

(Ex 120: TOF: 572.8 ± 105.34 vs. CTRL: 503.9 ± 100.95). Par ailleurs, une diminution progressive de la composante HF et inversement une augmentation de la composante LF était notée entre Ex 100 et Ex 120 chez les TOF mais non chez les CTRL ($p < 0.05$) (Ex 120: LF/HF: TOF: +120.7 ± 44.86 vs. CTRL: -21.8 ± 10.86, %). Ces observations ne peuvent s'expliquer par une différence de la fréquence respiratoire qui était strictement la même dans les deux groupes pour toutes les situations expérimentales. Ces résultats suggèrent une diminution de la variabilité sinusale de base ainsi qu'une perturbation des ajustements de la balance sympatho-vagale au cours de situations sympatho-excitatives chez les patients opérés pour TOF malgré l'excellence du statut clinique post-opératoire.

PART I: REVIEW OF LITERATURE

1.0 Circulatory Control in Patients Operated for Tetralogy of Fallot in Early Childhood

The long-term consequences of surgical repair of tetralogy of Fallot on the neurohumoral modulation of cardiovascular function remain poorly understood. While postoperative results of surgery are generally successful, evidence of residual cardiac disorders and rhythm disturbances as well as a low to normal exercise tolerance may be indicative of a potential dysregulation of circulatory function.

1.1 Incidence of Congenital Heart Defects and Tetralogy of Fallot

The incidence of congenital heart disease in the Western industrialized world has varied from a low value of 3 to 5 per 1000 live births to a high of 12 per 1000 live births (Hoffman, 1995). As a result of dramatic advances in diagnosis and treatment, particularly surgical repair, about 90% of these patients now live to adulthood (Perloff, 1991).

There are several structural malformations that can result during the development of the heart. Isolated ventricular septal defect is the most common malformation, occurring in approximately 28% of all patients with congenital disease. Other relatively common congenital disorders, in descending order of incidence are pulmonary stenosis (9.5%), patent ductus arteriosus (8.7%), ventricular septal defect with pulmonary stenosis including tetralogy of Fallot (6.8%), atrial septal defect (6.7%), aortic stenosis (4.4%), coarctation of the aorta (4.2%), atrioventricular canal including partial and complete (3.5%) and transposition of the great arteries (3.4%). These nine defects constitute nearly 75% of all congenital heart disease in infants and children (Nugent et al., 1994). Out of the previously listed diseases, tetralogy of Fallot is generally recognized to be the most common of the cyanotic cardiac malformations (Webb et al., 1996).

1.2 Tetralogy of Fallot and Associated Pathophysiological Implications and Consequences

Tetralogy of Fallot (TOF) is characterized by: a ventricular septal defect, an infundibular pulmonic stenosis, dextroposition of the aorta and right ventricular hypertrophy secondary to the right ventricular outflow tract obstructive lesion. The ventricular septal defect is usually large and is associated with equalization of left and right ventricular pressures. Although the degree of aortic overriding is quite variable, it has little effect on the underlying hemodynamic state. Thus, it is the extent of the subpulmonary stenosis that largely determines the clinical hemodynamic state of patients with TOF. The location of the right ventricular outflow tract obstruction can include the os infundibulum, pulmonary valve, or supravalvular pulmonary artery. A combination of infundibular and pulmonary valve stenosis is the most common type of obstruction, occurring in 74% of children with TOF (Kirklin & Barrett-Boyes, 1993).

Defects in the ventricular septum with obstruction to right ventricular outflow encompass a wide anatomic, physiological and clinical spectrum. The degree of right ventricular outflow tract obstruction varies from mild stenosis to complete pulmonary atresia. The direction and magnitude of pulmonary blood flow is determined by the degree of the right ventricular outflow tract obstruction, the presence and size of the ductus arteriosus or systemic-to-pulmonary artery collateral vessels and surgically created shunts. With mild obstruction, the presentation is of increased pulmonary blood flow and minimal cyanosis, so-called "pink tetralogy" or "acyanotic Fallot". Most young patients, however, have significant right ventricular outflow tract obstruction with a consequent right-to-left shunt. Thus, these patients will have cyanosis, erythrocytosis, dyspnea, and

fatigue. The degree of cyanosis and polycythemia is proportional to the pulmonary blood flow (Warnes et al., 1996). Moreover, in its most severe variant, TOF patients with pulmonary atresia often exhibit the development of large systemic collateral vessels providing pulmonary blood flow (Epstein, 1994).

The natural history of unrepaired TOF is heavily influenced by the severity of the autonomic defect (Kirklin & Barrett-Boyes, 1993). Statistics demonstrate a 25% mortality rate by 1 year of age that increases to 40% by 3 years. Only 30% of patients can be expected to reach 10 years of age, and not more than 5% to live to reach 40 years (Bertranou et al., 1978; Kirklin & Barrett-Boyes, 1993). Patients with TOF and pulmonary atresia have an even worse prognosis for survival without surgical intervention, with a mortality that approaches 50% in the first year of life and can be as high as 84% by 5 years of age (Kirklin & Barrett-Boyes, 1993). Presently, with advances in cardiological diagnosis and management, the majority of cases are detected and repaired in early childhood.

1.3 Surgical Treatment

The surgical treatment of TOF requires a choice between total correction or palliation. Some patients with TOF appear to be poor candidates for initial correction due to poor development of the pulmonary arterial tree. Palliative surgery in the form of a systemic to pulmonary shunt may relieve hypoxia by improving pulmonary blood flow. In addition, it may facilitate growth of hypoplastic pulmonary arteries, therefore providing a more favourable opportunity for successful total intracardiac repair. Various systemic-to-pulmonary artery shunts have been used, including subclavian artery-to-pulmonary artery (Blalock-Taussig), descending aorta-to-left pulmonary artery (Potts), and ascending aorta-

to-right pulmonary artery (Waterston) anastomoses. The Blalock-Taussig shunt is now the preferred procedure for palliation in most institutions. Yet palliation followed by repair has become less common in most centers, which currently offer primary repair in infancy as the treatment of choice.

It was only in 1954, nearly forty-five years ago that C. Walton Lillehei and his team successfully performed the first complete repair of TOF at the University of Minnesota (Lillehei et al., 1955). Since then total corrective surgery has been refined and modified. It is usually performed at 6 to 18 months of age (Edwards, 1996) where indications for surgical intervention include decreased exercise tolerance, hypercyanotic spells, excessively high hemoglobin and hematocrit (approaching 65%) (Nugent et al., 1994), or the attainment of an appropriate age and size for elective repair.

Intracardiac repair consists of closure of the ventricular septal defect and relief of the pulmonary stenosis. This entails the performance of several procedures which may include the takedown of previous shunts, a right atriotomy or if not possible, a right ventriculotomy, patch closure of the ventricular septal defect, resection of the infundibular myocardium, a possible pulmonary valvotomy, path reconstruction of the annulus and right ventricular outflow tract with an infundibular or transannular patch of Dacron, Teflon or pericardium.

1.4 Post-Surgical Clinical Status

The post-operative prognosis following complete repair of TOF is good, especially when surgical treatment is performed in childhood. Patients are able to lead productive and "normal" lives. Early postoperative mortality is less than 5%, and late deaths claim an additional 5% of patients by 20 years after operation (Edwards, 1989; Kirklin & Barrett-Boyes, 1993). Although corrective surgery greatly improves a patient's prognosis, by attempting to restore "normal" physiological function if not "normal" anatomical structure, residual hemodynamic abnormalities are common.

Abnormalities such as residual pulmonary stenosis, pulmonary regurgitation (pulmonary valve insufficiency), right ventricular dysfunction, residual ventricular septal defect and arrhythmias are inherent to the surgical procedure itself.

Incomplete relief of the outflow tract obstruction and/or narrowing at an area of the repaired site may result in residual right ventricular outflow tract obstruction. It remains the most common complication of corrective surgery requiring reoperation, occurring in 1-5% of children undergoing total repair (Kirklin et al., 1989; Lillehei et al., 1986; Touati et al., 1990). Placement of an outflow tract patch across the pulmonary valve annulus to relieve the pulmonary stenosis frequently results in pulmonary valve insufficiency. Pulmonary insufficiency occurs in up to 78% of children operated on for TOF (Horneffer et al., 1990). Mild to moderate pulmonary insufficiency is well tolerated for many years, but right ventricular failure eventually occurs because of chronic volume and pressure overload (Carvalho et al., 1992; Finck et al., 1988). Long-term follow-up has shown that right ventricle dysfunction may recover sufficiently if progressive pulmonary regurgitation is prevented by inserting a pulmonary valve prosthesis (Bove et

al., 1985). Additionally, tricuspid insufficiency may be present due to annular dilatation or distortion of tricuspid septal leaflets.

Arrhythmias are a common finding in patients operated for TOF (Perry & Garson, 1995). The incidence of late sudden death secondary to malignant ventricular arrhythmias (Deanfield et al., 1984) after repair of TOF is estimated at approximately 1.4 to 4.9% (Chander et al., 1990; Walsh et al., 1988; Zhao et al., 1985). In most cases however, the main electrophysiological consequence is that of condition disturbances such as right bundle branch block may be observed in over 90% of patients operated for TOF (Walsh et al., 1988) as a consequence of the surgical procedures and placement of a ventricular septal defect patch (Epstein, 1994). Acquired left anterior hemiblock suggests damage to the central portion of the atrioventricular specialized conduction system during placement of the ventricular septal defect patch (Epstein, 1994). Another evidence of conduction disturbances may be found in the abnormally low heart rate often reported in these patients in response to maximal dynamic exercise.

1.5 Response to Dynamic Exercise in Surgically Corrected Tetralogy of Fallot

Over the last 20 years, several studies have looked at the response to maximal dynamic cycling or treadmill exercise in young surgically corrected TOF patients in comparison to age-matched controls (Table 1). TOF patients' general characteristics were as follows: age ranged between 8.9 and 15.9 years, the post-operative period ranged between 3.8 to 10.9 years and were classified either on the basis of hemodynamic results following catherization or differentiating levels of pulmonary regurgitation.

Table 1. Response to maximal dynamic exercise in control subjects and surgically corrected tetralogy of Fallot patients.

Study	Subjects/n	Age (y)	Post-op (y)	Mode T/C	VO_2 max (mL/kg/min)	HR max (bpm)	Δ HR (bpm)
Bouhour et al. (1984)	CTRL/11	11.3(2.3)		T	1.59(0.22)[6]	194(8)	
	TOF/12	10.3(2.2)	7.5	T	1.05(0.18)[6]***	175(16)***	19
Carvalho et al. (1992)	CTRL/12			T	52.0(7.1)	197(6)	
	TOF/12	11.6(2.8)	(5.4-12.7)	T	48.0(8.8)	180(17)**	17
Guillaumont et al. (1996)	CTRL/10	11.2(3.1)		C	41.5(5.6)	180.3(13.1)	
	TOF/8	12.7(4.1)	NA	C	41.4(8.4)	169.5(23.1)	10.8
Lambert et al. (1980)	CTRL/29	15.4(5.1)		T	43.1(9.0)	194(7)	
	TOF/68	15.6(5.3)	5.6(3.0)	T	36.3(7.5)**	184(15)**	10
Marx et al. (1988)	CTRL/15	12		C	39.0(7.9)	182(17)	
	TOF/7[1]	12	NA	C	37.0(8.2)	178(12)	4
	TOF/6[2]	12		C	28.0(6.1)***	172(15)	10
	TOF/6[3]	10		C	25.0(4.8)***	155(11)**	27
Perrault et al. (1989)	CTRL/10	15.8(1.6)		C	41.3(6.0)	191(12)	
	TOF/13	15.9(1.9)	10.9	C	37.6(10.0)	178(14)**	13
Takahashi et al. (1986)	CTRL/96			T	43.4(7.1)	191(11)	
	TOF/12[4]	8.9(2.1)	3.8(2.1)	T	28.0(9.5)***	177(12)**	14
	TOF/9[5]			T	40.3(7.8)	177(6)**	14
Tomassoni et al. (1991)	CTRL/20	10.2(2.5)		T	37.53(2.45)	184.5(2.9)	
	TOF/20	9.9(2.9)	6.9	T	34.10(2.98)	173.8(4.6)*	10.7

CTRL= control subjects; TOF= tetralogy of Fallot patients; Post-op= time interval between total correction and exercise evaluation; Mode of evaluation: T= treadmill, C= cycle ergometer. VO_2 max= maximal oxygen consumption; HR max= maximal heart rate in beats per minute (bpm); ΔHR = difference in maximal heart rate between control subjects and tetralogy of Fallot patients; 1 indicates TOF patients with mild pulmonary regurgitation (PR); 2 indicates TOF patients with moderate PR; 3 indicates TOF patients with severe PR; 4 indicates TOF patients with poor hemodynamic results following cardiac catherization; 5 indicates TOF patients with good hemodynamic results following cardiac catherization; 6 indicates that value is expressed in L/min/m²; NA= not available.

* $p < 0.10$, ** $p < 0.05$, *** $p < 0.001$ TOF vs. CTRL

Tetralogy of Fallot patients with poor hemodynamic status or moderate to severe pulmonary regurgitation generally displayed significantly lower maximal oxygen consumption ($V0_2max$) (Bouhour et al., 1984; Lambert et al., 1980; Marx et al., 1988; Takahashi et al., 1986) than controls. Differences between patients and controls ranged between 15.8 and 35.9 %. Studies examining young patients operated on in early childhood and exhibiting excellent clinical or with only mild pulmonary regurgitation generally showed $V0_2max$ values similar to those of age-matched healthy control subjects (Carvalho et al., 1992; Guillaumont et al., 1996; Marx et al., 1988; Perrault et al., 1989; Takahashi et al., 1986).

Despite the normal maximal exercise tolerance observed in these patients, closer examination reveals abnormal hemodynamic responses to maximal dynamic exercise. There exists a limited number of studies examining the cardiac output response to exercise after repair of TOF. In two investigations of post-operative patients with good clinical status, CO_2 (Perrault et al., 1989) and acetylene (Tomassoni et al., 1991) rebreathing methods and determinations at submaximal and maximal exercise intensities revealed lower cardiac output in patients with TOF despite normal $V0_2max$ values. These observations thus suggest that in order to attain similar $V0_2max$ values, patients with TOF demonstrate elevated arteriovenous oxygen extraction than age-matched healthy children, thus compensating for the lower cardiac output (Perrault et al., 1989).

In patients with significant pulmonary insufficiency or residual pulmonary stenosis resulting in a reduced maximal oxygen consumption, the abnormally low cardiac output may be explained by an impairment in left and right ventricular function. Kondo

et al. (1995) demonstrated latent left ventricular dysfunction during semi-upright cycling exercise related to an enlarged right ventricle primarily due to pulmonary regurgitaion following repair of TOF. Using radionuclide first-pass ventriculography, after long-term repair (16 ± 2) years in TOF patients, they found significant differences during rest and exercise in end-diastolic, end-systolic and stroke volumes in both the right and left ventricles. Although left ventricular ejection fraction increased from rest to exercise in both TOF and controls, the increment of ejection fraction on exercise was significantly attenuated in both ventricles in TOF patients compared to control subjects. Recent data however indicate that restoration of the pulmonary valve with cryopreserved allografts or the use of a modified transatrial ventricular septal defect closure and infundibular incision avoiding muscle resection and patch expansion of the right ventricular outflow tract improved maximal exercise tolerance (Attalah-Yunes et al. 1996; Warner et al. 1993). These observations suggest that newer modified surgical techniques for the repair of TOF might improve the hemodynamic responses. Measurements of exercise cardiac output in patients operated using these newer techniques are not yet available.

A common finding in the low cardiac output of patients with both normal and abnormal $V0_2max$ is an abnormally low maximal heart rate. Patients operated for TOF consistently show maximal heart rates 4 to 27 beats per minute (bpm) lower than aged-matched controls. In patients with normal maximal oxygen uptake the lower cardiac output reported may be related to a maximal heart rate lower than control subjects with an average difference of 11.6 bpm may be calculated (Table 1). The explanation for this chronotropic limitation remains unclear although it has generally been assumed to be the result of a sympathetic dysfunction (Driscoll et al., 1987).

2.0 Assessment of Sympathovagal Function in Humans

The efferent autonomic signals are transmitted through both the sympathetic and parasympathetic divisions of the nervous system. There are a number of methods that attempt to quantify or estimate sympathetic activity such as measurements of urine, circulating or cerebrospinal fluid catecholamines as well as direct nerve recordings.

There are two modern assay techniques used to measure catecholamines in tissue, media, cerebrospinal fluid, and blood. One technique, the microradioenzymatic assay takes advantage of the fact that the catecholamines are methylated in vivo. Dopamine, norepinephrine and epinephrine are O-methylated in vivo to form methooxytyramine, normetanephrine and metanephrine respectively. Radioenzymatic assays exploit these metabolic fates by incorporating ^{3}H into the structure of the O-methylated derivatives. This is accomplished by using the enzyme catechol-O-methyl transferase (COMT) and as a methyl donor, ^{3}H-S-adenosyl methionine (^{3}H-SAM). By using thin layer chromatography, the amount of catecholamines can be assessed due to the amount of the tritiated methylated products (i.e., methoxytyramine, normetanephrine, metanephrine) is proportional to the amount of the respective starting substrate (i.e., dopamine, norepinephrine and epinephrine) (Freeman, 1995).

The other widespread approach to quantitating catecholamines is through the use of high-performance liquid chromatography coupled with electrochemical detection (HPLC-EC). Using this technique, the separation of catecholamines is achieved with an analytical column packed with C_{18}-reverse material. This material allows resolution of catecholamines, their precursors and metabolites. Resolution of sample molecules takes place by their differential interactions with the mobile-phase solvent and the column

packing material. Distinct bands of solute form during passage through the column. Resolution of the solutes is controlled by pH, ionic strength, the nature and concentration of aqueous phase, and the concentration of the organic components of the mobile organic phase. Quantitation is achieved by eluting the resolved solutes through the electrochemical detector. The potential applied to the detector's cell favors oxidation of the catecholamine. For a given set of operating conditions, the oxidative current is directly proportional to the concentration of electroactive species in solution (Freeman, 1995).

The main limitation with catecholamine determination is that measurement of plasma catecholamines can only provide a rough approximation of overall sympathetic nervous system activity because circulating or urinary values are influenced by the rate of release and clearance from different vascular beds. In addition, plasma catecholamine levels do not enable examination of specific autonomic influences, and thus may poorly reflect cardiac sympathetic activity.

Another method to assess sympathetic tone is muscle sympathetic nerve activity (MSNA). By using microneurography, the control of sympathetic-vasoconstrictor nerve activity to resistance vessels in non-active skeletal muscle can be estimated both under resting as well as exercising conditions. Direct intraneural, continuous measurements of MSNA can be obtained using the microneurographic technique developed by Hagbarth and colleagues in the late 1960's (Vallbo et al., 1979). For instance, during leg cycling exercise, MSNA can be recorded from a non-active muscle group, for example, through the median nerve at the elbow. MSNA would be recorded from sympathetic nerve fascicles to muscle blood vessels within the median nerve. A thin tungsten electrode is

inserted percutaneously into sympathetic fascicles and MSNA can be quantified from the integrated neurogram by burst frequency and the average area of bursts/time (min). "Total minute activity" can then be calculated as the product of the burst frequency and average amplitude (area) (Seals & Victor, 1991).

The limitations to MSNA is that it is somewhat of an invasive procedure, highly experienced persons are needed to obtain accurate readings, the limb of the impaled nerve must remain relaxed, consequently measurements of MSNA to contracting muscles are not possible. Furthermore, MSNA responses to exercise are based solely on measurement of sympathetic discharge targeted specifically to inactive skeletal muscle vasculature, which may not be representative of sympathetic discharge to other regional circulations or the heart. Without simultaneous measurements of end-organ responses, a direct relationship between sympathetic activity and vascular resistance cannot be assumed in every exercise condition (Seals & Victor, 1991).

Recently a non-invasive procedure to assess sympathovagal balance of the heart and arterial vessel sympathetic tone has received much attention both for clinical and research purposes. With the versatility of digital computers, modern signal processing techniques are now commonly used to investigate beat-to-beat fluctuations in R-R intervals or arterial blood pressure (heart rate and blood pressure variability) reflecting sympathetic and parasympathetic influences on the SA node and fluctuations of sympathetic activity of resistive vessels.

3.0 Heart Rate Variability

The control of heart rate depends on the interaction of efferent sympathetic and parasympathetic influences on the sinus node. The parasympathetic influence via the vagus nerve opposes the sympathetic influence via cervical postganglionic sympathetic fibers and circulating catecholamines (Jacobsen & Garson, 1990). Under resting conditions, sinus arrhythmia is a normal phenomenon. Sinus arrhythmia is the variations in successive R-R intervals that commonly occur as the result of variations in the vagal tone caused by the respiratory cycle; R-R interval shortening during inspiration and lengthening as a result of expiration (Jacobsen & Garson, 1990). These fluctuations in R-R intervals result from the influences of central command as well as mechanical influences of respiration on arterial and cardiopulmonary baroreflexes (Saul, 1990). Under quiet breathing conditions, respiratory activity is the primary modulator of heart rate fluctuations through a complex lung-heart interaction (Saul, 1990). Respiratory sinus arrhythmia is thus composed of an effect of respiration on heart rate such that spontaneous fluctuations of heart rate are synchronized with breathing frequencies. An increase in heart rate is generally seen during inspiration with a deceleration during expiration. Although cardiac sympathetic efferent nerve fibers may contribute, they are not essential for the phenomenon to occur, as shown in results from animal studies indicating rhythmic changes in cardiac vagal efferent fibers to be the primary component (Akselrod et al., 1981; Akselrod et al., 1985; Katona & Jih, 1975).

Heart rate variability (HRV) provides a measure of the periodic changes in successive R-R intervals of the electrocardiogram. For a given electrocardiographic signal sequence, the overall magnitude of HRV can be quantified in the time domain, using

simple statistics such as the standard deviation of the R-R or using a mathematical function such as the Fast Fourier Transform, the spectrum of the extent to which R-R variations are occurring at different frequencies can be obtained. Three typical peaks in the HRV spectrum have been identified corresponding to: a) a peak at the respiratory frequency corresponding to sinus arrhythmia defined as the high frequency (HF) component and therefore reflecting the parasympathetic involvement which central position is observed at the respiratory frequencies (usually > 0.15 Hz under normal quiet breathing) b) a low-frequency (LF) component which central position can be exhibited around 0.1 Hz, and can be related to both parasympathetic and sympathetic nervous involvement and a very low frequency component (VLF) centered around 0.04 Hz thought to be related to peripheral vasomotor regulation (Akselrod et al., 1981; Pagani et al., 1986; Pomeranz et al., 1985; Saul, 1990). The LF component increases in the presence of increased sympathetic activity. The variance in each of the two components and their ratio, LF/HF can therefore be chosen as a noninvasive measure of sympathovagal interactions (Pagani et al., 1986; Pomeranz et al., 1985).

For example, responses to hemodynamic stressors such as head-up passive tilt at 90°, standing, mental stress and physical exercise tend to shift the sympathovagal balance towards sympathetic predominance increasing the extent of the LF component contribution to HRV (Furlan et al., 1987; Pagani et al., 1986; Pagani et al., 1991; Pagani et al., 1988). In animal studies, the LF component was increased by coronary or carotid artery occlusion and physical exercise. Under all of these experimental conditions a shift in the LF/HF ratio towards sympathetic predominance was observed and the increase in the LF spectral power component was accompanied by a decrease in the HF spectral

power component (Rimoldi et al., 1990a; Rimoldi et al., 1990b). Conversely, other maneuvers used to increase vagal tone or the HF component include controlled respiration, water immersion of the face and head down tilt (Malliani et al., 1990; Pagani et al., 1986).

3.1 Heart Rate Variability in Healthy and Diseased State

Heart rate variability studies have employed both long-term and short-term recordings in healthy and diseased populations. The selection of which method used is based on the goal of each particular study. Long-term recordings performed over a 24-hour period using Holter monitoring provide information of averages over the entire 24-hour period or specific time intervals of autonomic modulations reflected by the HF and LF spectral components. Such recordings may provide insight as to circadian differences in the HF or LF components, effectiveness of drug treatments, or may help establish risk stratification such as in patients after an acute myocardial infarction or clinical assessments for diabetic neuropathy. Unlike long-term recordings, studies using short-term recordings are performed under standardized conditions, where subjects are usually subjected to orthostatic and autonomic nervous system stress such as resulting from head-up tilting, isometric and dynamic exercise. According to the most recent recommendations from the "Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology" (Malik et al., 1996), the energy measurement resulting from the summation of power components over a frequency window centred over either the VLF, LF, and HF should be reported in normalized units (nu) which represents the relative energy of one component in proportion to the total energy minus the VLF component as well as absolute values (ms^2) in order to completely describe the distribution of energy in spectral components. Although energy is the more appropriate term to express the summation of power components over a frequency window

centered over either HF or LF, the term power is used throughout this thesis to reflect "energy" as is commonly used in the medical literature. The intent of the present review being to examine the autonomic responses to various stressors, studies primarily using short-term recordings for HRV assessment will be presented.

3.2 Conditions of Quiet Rest with Spontaneous Breathing

Results of the HF and LF components and the LF/HF ratio of R-R variability obtained under resting conditions in the supine or seated conditions in healthy adult populations as well as patients after myocardial infarction or heart transplantation, or suffering from atrioventricular tachycardia, hypertension, diabetes and various other conditions are shown in Table 2. Subjects generally ranged in age between 16 and 94 years. With studies employing normalized units (nu), control subjects showed HF values to range between 24.0 and 69.5 nu, with an average calculated mean of 42.3 nu. Overall, patients had HF values ranging from 17.0 to 63.7 nu, with a grand mean of 37.4 nu, which was slightly lower than controls. The LF component showed control subjects' values ranging between 25.6 to 62.2 nu, with a calculated mean of 48.0 nu. Patients showed LF values ranging from 12.5 to 69.5 nu, with a mean of 52.7 nu, which was marginally higher than controls. Consequently, patients had a higher overall mean in LF/HF ratio than controls (2.9, range (0.3-8.0)), patients vs. (1.7, range (0.54-3.69), controls). When the percentage of HF over the total power (HF and LF components only) was calculated, regardless of how power was expressed, similar values were observed for both groups. The grand mean percentage for the HF spectral power component for control subjects was 44.7%, range (25.3-70.0%) and 41.1%, range (19.8-83.6%) for patients.

Table 2. **Spectral components of HF, LF and LF/HF ratio of R-R variability during resting conditions with spontaneous breathing in control subjects and patient populations.**

Study	Subjects/N	Age (y)	Baseline Position	HF Power (nu)	LF Power (nu)	LF/HF Ratio	% HF Power
Bernardi et al. (1990)	CTRL/9	23.1(0.7)	Sit	44.0(4.0)	56.0(4.0)	NA	44.0
	HTX/6	48.3(3.1)		1.17(0.22)[1]	0[1]		
Casadei et al. (1995)	CTRL/11	21.1(0.4)	Sit	37.6(8.3)	53.1(8.0)	NA	41.5
Dixon et al. (1992)	CTRL/14	27.4(2.6)	Supine	43.7(22.4)[2]	69.6(19.5)[2]	1.60(0.85)	38.6
Furlan et al. (1993)	CTRL/29	16.0(0.4)	Supine	53.1(2.6)	37.4(2.9)	0.78(0.07)	58.7
Guzzetti et al. (1991)	CTRL/12	39(4)	Supine	44.2(4.2)	49.1(5.7)	NA	47.4
	CC(1)/7	40(4)		43.0(7.6)	52.9(8.7)		44.8
	CC(2)/12	51(4)		51.6(6.0)	37.1(7.1)		58.2
Guzzetti et al. (1994)	CTRL/15	34(3)	Supine	41(4)	51(3)	1.55(0.25)	44.6
	QUAD/8	33(4)		56(5)	35(5)	0.70(0.14)	61.5
Hartikainen et al. (1997)	CTRL/14	33.1(2.6)	Supine	51(4)	49(4)	1.22(0.27)	51.0
	AVNRT/17	36.8(3.4)		51(5)	49(5)	1.35(0.29)	51.0
	AVRT/14	35.0(3.4)		39(5)	61(5)	3.26(1.27)	39.0
Kamath et al. (1991)	CTRL/19	(20-32)	Supine	41.7(20.0)[2]	68.4(18.9)[2]	2.1(1.2)	37.9
Lipsitz et al. (1990)	CTRL/12	(18-35)	Supine	1.27(1.07)[3]	1.34(0.84)[3]	NA	48.7
	CTRL/10	(71-94)		0.19(0.09)[3]	0.30(0.16)[3]		38.8
Lombardi et al. (1987)	CTRL/26	NA	Supine	35(3)	53(3)	2.0(0.3)	39.8
	MI(1)/70	54(2)		17(1)	69(2)	8.0(1.1)	19.8
	MI(2)/33			23(2)	62(2)	4.0(0.6)	27.1
	MI(3)/29			30(2)	54(3)	3.0(0.7)	35.7
Lombardi et al. (1992)	VA/13	NA	Supine	39(6)	52(6)	1.98(0.45)	42.9
Lucini et al. (1994)	N/63	31(2)	Supine	37(2)	53(2)	2(1)	41.1
	HYP/78	48(1)		31(2)	60(2)	3(1)	34.1
Montano et al. (1994)	CTRL/22	(22-66)	Supine	−47.2	−34.4	−0.97	57.8
Morillo et al. (1994)	CTRL/15	34(12)	Supine	2.2(0.6)[4]	6.4(0.7)[4]	2.1(1.2)	25.6
	-HUT/15	33.5(13)		2.3(0.7)[4]	6.1(0.8)[4]	2.2(0.8)	27.4
	+HUT/15	32(14)		2.4(0.8)[4]	5.2(0.9)[4]	2.4(0.8)	31.6
Pagani et al. (1991)	CTRL/10	22(1)	Supine	46(6)	44(6)	1.4(0.4)	51.1

Table 2. Continued

Study	Subjects/N	Age (y)	Baseline Position	HF Power (nu)	LF Power (nu)	LF/HF Ratio	% HF Power
Pagani et al. (1986)	CTRL/30	(20-30)	Supine	24.0(2.0)	58.2(3.3)	3.62(0.70)	29.2
	CTRL/10	(30-45)		26.3(4.3)	62.2(6.3)	3.69(1.23)	29.7
	CTRL/17	(45-60)		32.0(4.6)	49.9(4.9)	2.58(0.61)	39.1
Piccirillo et al. (1996)	N/9	38(13)	Supine	69.5(16.6)	31.4(15.2)	0.54(0.29)	68.9
	HYP/14	41(9)		30.7(13.7)	69.3(13.7)	3.2(2.6)	30.7
Pitzalis et al. (1996)	CTRL/18	28(2)	Supine	39.7(14.5)	60.3(14.5)	1.83(0.96)	39.7
Sanderson et al. (1996)	CTRL/9	45(2)	Supine	59.8(9.0)	25.6(8.6)	0.6(0.2)	70.0
	CHF/11	57(15)		63.7(5.4)	12.5(5.4)	0.3(0.1)	83.6
Thomaseth et al. (1990)	CTRL/10	36.1(6.7)	Supine	347(72)[3]	1024(218)[3]	NA	25.3
	D/10	42.6(12.5)		12(2)[3]	18(8)[3]		40.0
Veglio et al. (1995)	N/10	50(5)	Supine	32.0(2.6)	49.0(2.6)	1.62(0.10)	39.5
	EH/11	51(3)		22.7(4.5)	69.5(5.4)	5.4(1.5)	24.6
	IHA/10	52(3.7)		32.3(4.7)	54.5(5.8)	2.1(0.4)	37.2
	APA/7	51.5(3.9)		30.4(4.8)	52.6(7.9)	2.03(0.5)	36.6
Yamamoto et al. (1991)	CTRL/6	22(3)	Sit	4230.2(598.71)[1]	2285.7(901.03)[1]	0.58(0.26)	64.9

CTRL= control subjects; HTX= heart transplant patients; CC(1)= chronic Chagas' disease patients with only positive serology; CC(2)= chronic Chagas' patients with positive serology and ECG abnormalities; QUAD= quadriplegic patients; AVNRT= atrioventricular nodal reentrant tachycardia patients; AVRT= orthodromic atrioventricular reentrant tachycardia patients; MI(1)= myocardial infarction patients at 2 weeks; MI(2)= myocardial infarction patients at 6 months; MI(3)= myocardial infarction patients at 12 months; VA= ventricular arrhythmia patients; N= normotensive subjects; HYP= hypertensive subjects; -HUT= syncope patients with a negative tilt response; +HUT= syncope patients with a positive tilt response; CHF= congestive heart failure patients; D= diabetic patients; EH= essential hypertensive patients; IHA= idiopathic hyperaldosteronism patients; APA= aldosterone producing adenoma patients; nu= normalized units; 1= ms^2; 2= $bpm^2 \bullet Hz^{-1}$; 3= arbitrary units; 4= ln bpm^2; % HF Power= % HF power of total (HF and LF components); NA= not available.
Mean (SEM)

Overall at rest, patient populations seem to have similar values in the HF and LF spectral power components to control subjects. However, significant group differences in either of the spectral components have been reported. Hypertensive and essential hypertensive patients displayed a significantly greater ($p < 0.05$) LF component and thus a lower percentage of HF power than their normotensive counterparts: (34.1 vs. 41.1%) (Lucini et al., 1994), (30.7 vs. 68.9%) (Piccirillo et al., 1996) and (24.6 vs. 39.5%) (Veglio et al., 1995). Diabetic patients showed significantly lower ($p < 0.001$) values in both the HF and LF components than control subjects (Thomaseth et al.,1990). Patients with orthodromic atrioventricular reentrant tachycardia displayed a significantly lower HF component (39 ± 5 vs. 51 ± 4, nu) and a higher LF component (61 ± 5 vs. 49 ± 4, nu) than controls ($p < 0.05$) (Hartikainen et al., 1997). Following heart transplantation, Bernardi et al. (1990) observed no LF power in recipients. Two weeks following a myocardial infarction, patients showed a significantly lower HF component (17 ± 1 vs. 35 ± 3, nu) and subsequently a higher LF component (69 ± 2 vs. 53 ± 3, nu) and LF/HF ratio (8 ± 1.1 vs. 2 ± 0.3) than controls ($p < 0.05$). In addition, the longer the period after a myocardial infarction (2 weeks vs. 6 months vs. 12 months), the greater the HF component (7 vs. 23 vs. 30, nu) suggesting the reappearance of vagal influence (Lombardi et al., 1987).

It has been documented that age plays a role in the integrity of the autonomic nervous system. With aging, there is an attenuation of respiratory sinus arrhythmia, thus a decrease in parasympathetic activity to the heart (Lipsitz et al., 1990; Shannon et al., 1987). This may explain in part studies in which controls had a higher HF than LF component. Controls aged 16.0 ± 0.4 years had a percentage of HF power of 58.7% (Furlan et al.,1993) and a percentage of HF power of 64.9% when aged 22 ± 3 years (Yamamoto et al.,1991).

3.3 Effects of Controlled Respiration

High frequency variations are produced by respiratory sinus arrhythmia and essentially due to the rapidly varying vagal influence on the sinus node (Akselrod et al., 1981; Pomeranz et al., 1985). When imposing a breathing frequency the occurrence of R-R variations in synchrony with respiration rate is thus predictable and consequently, controlled breathing may be used to standardize the frequency band at which the greater proportion of heart rate variations will be found and thus the greater spectral power component. Since common resting breathing rates occur at frequencies comprised in the standard HF band, controlling respiration will result in an increase in the power of the HF spectral component at the expense of the LF component.

Tables 3A, 3B, and 3C summarize the effect of controlled on the HF, LF components and the LF/HF ratio of HRV spectral analysis in control subjects and patient populations, respectively.

As expected, studies with control subjects lying down quietly and asked to control respiratory rate at various frequencies (0.17, 0.25-0.27, and 0.33 Hz), resulted in an increase in the HF component by an average of 35.5%, range (12.0-89.0%), except for Cooke et al. (1998), in which HF decreased by 48.4%. The reason for the decrease in the HF component may be two-fold: with controlled respiration the total power is expected to increase, yet the total power decreased from 4800 ± 1500 ms^2 with normal breathing to 2800 ± 400 ms^2 with a set breathing rate of 0.25 Hz. Secondly, when the spectral components are expressed in ms^2, the changes in total power influence both HF and LF in the same direction and prevent the appreciation of the fractional distribution of the spectrum (Malik et al., 1996). The LF component decreased by an average of 26.5%,

Table 3. Effect of controlled respiration on spectral components of R-R variability in control subjects and patient populations.

A) High frequency component

Study	Subjects/ N	Age (y)	Position	Imposed Breathing Rate (Hz)	HF Power with SR (nu)	HF Power with CR (nu)	% Change
Cooke et al. (1998)	CTRL/10	25.5(1.7)	Supine	0.25	3100(900)[1]	1600(400)[1]	-48.4
Guzzetti et al. (1994)	CTRL/15	34(3)	Supine	0.33	41(4)	46(4)	+12.2
	QUAD/8	33(4)			56(5)	66(6)	+17.9
Hayano et al. (1991)	CTRL/15	(21-24)	Supine	0.25	NA	58(18)	
Pagani et al. (1986)	CTRL/16	(20-60)	Supine	0.33	27.3(2.7)	51.6(4.4)	+89.0
			90° HUT		7.8(1.4)	15.3(3.0)	+96.2
Pitzalis et al. (1996)	CTRL/18	28(2)	Supine	0.27	39.7(14.5)	58.2(18.0)	+46.6
Pomeranz et al. (1985)	CTRL/6	(22-36)	Supine	0.25	NA	0.065(0.02)[2]	
Sanderson et al. (1996)	CTRL/9	45(2)	Supine	0.17	59.8(9.0)	79.4(6.3)	+32.8
				0.25		68.0(5.7)	+13.7
				0.33		70.9(7.1)	+18.6
			Stand	0.17	22.7(9.6)	63.8(8.5)	+181.1
				0.25		51.2(7.7)	+125.6
				0.33		25.3(4.8)	+11.4
	CHF/11	57(15)	Supine	0.17	63.7(5.4)	74.0(7.7)	+16.2
				0.25		58.5(6.0)	-8.2
				0.33		64.0(5.0)	+0.5
			Stand	0.17	64.3(8.0)	66.1(6.4)	+2.8
				0.25		52.0(5.7)	-19.1
				0.33		54.1(7.7)	-15.9
Vybiral et al. (1989)	CTRL/17	29(7)	Supine	0.25	NA	5205(3936)[3]	

CTRL= control subjects; QUAD= quadriplegic patients; CHF= congestive heart failure patients; HUT= head-up tilt; SR= spontaneous respiration; CR= controlled respiration; nu= normalized units; 1= ms^2 ; 2= $bpm^2 \bullet Hz^{-1}$; 3= arbitrary units; NA= not available; % Change= percentage change from spontaneous respiration.
Mean (SEM)

Table 3. **Effect of controlled respiration on spectral components of R-R variability in control subjects and patient populations.**

B) Low frequency component

Study	Subjects/ N	Age (y)	Position	Imposed Breathing Rate (Hz)	LF Power with SR (nu)	LF Power with CR (nu)	% Change
Cooke et al. (1998)	CTRL/10	25.5(1.7)	Supine	0.25	1600(300)[1]	1200(200)[1]	-25.0
Guzzetti et al. (1994)	CTRL/15	34(3)	Supine	0.33	51(3)	44(3)	-13.7
	QUAD/8	33(4)			35(5)	23(7)	-34.3
Hayano et al. (1991)	CTRL/15	(21-24)	Supine	0.25	NA	29(16)	
Pagani et al. (1986)	CTRL/16	(20-60)	Supine	0.33	56.2(3.9)	28.9(4.3)	-48.6
			90° HUT		86.4(2.9)	71.6(5.3)	-17.1
Pitzalis et al. (1996)	CTRL/18	28(2)	Supine	0.27	60.3(14.5)	41.8(18.0)	-30.7
Pomeranz et al. (1985)	CTRL/6	(22-36)	Supine	0.25	NA	0.033(0.008)[2]	
Sanderson et al. (1996)	CTRL/9	45(2)	Supine	0.17	25.6(8.6)	15.6(6.4)	-39.1
				0.25		22.7(5.2)	-11.3
				0.33		21.2(7.4)	-17.2
			Stand	0.17	59.3(10.5)	33.4(8.8)	-43.7
				0.25		37.3(9.1)	-37.1
				0.33		65.9(7.1)	+11.1
	CHF/11	57(15)	Supine	0.17	12.5(5.4)	10.7(5.2)	-14.4
				0.25		19.2(5.0)	+53.6
				0.33		16.4(3.6)	+31.2
			Stand	0.17	8.1(4.7)	15.0(7.1)	+85.2
				0.25		21.0(6.2)	+159.3
				0.33		25.6(9.3)	+216.0
Vybiral et al. (1989)	CTRL/17	29(7)	Supine	0.25	NA	4755(3654)[3]	

CTRL= control subjects; QUAD= quadriplegic patients; CHF= congestive heart failure patients; HUT= head-up tilt; SR= spontaneous respiration; CR= controlled respiration; nu= normalized units; 1= ms^2; 2= $bpm^2 \bullet Hz^{-1}$; 3= arbitrary units; NA= not available; % Change= % change from spontaneous respiration. Mean (SEM)

Table 3. Effect of controlled respiration on spectral components of R-R variability in control subjects and patient populations.

C) LF/HF ratio

Study	Subjects/N	Age (y)	Position	Imposed Breathing Rate (Hz)	LF/HF with SR	LF/HF with CR	% Change
Guzzetti et al. (1994)	CTRL/15	34(3)	Supine	0.33	1.55(0.25)	1.14(0.18)	-26.4
	QUAD/8	33(4)			0.70(0.14)	0.54(0.27)	-22.8
Pagani et al. (1986)	CTRL/16	(20-60)	Supine	0.33	2.5(0.3)	0.7(0.1)	-72.0
			90° HUT		16.0(3.0)	8.3(1.6)	-48.1
Pitzalis et al. (1996)	CTRL/18	28(2)	Supine	0.27	1.83(0.96)	0.89(0.65)	-51.4
Sanderson et al. (1996)	CTRL/9	45(2)	Supine	0.17	0.6(0.2)	0.3(0.1)	-50.0
				0.25		0.4(0.1)	-33.3
				0.33		0.4(0.2)	-33.3
			Stand	0.17	4.7(0.3)	0.8(0.3)	-83.0
				0.25		1.3(0.5)	-72.3
				0.33		4.3(1.4)	-8.5
	CHF/11	57(15)	Supine	0.17	0.3(0.1)	0.3(0.2)	0
				0.25		0.4(0.1)	+33.3
				0.33		0.3(0.1)	0
			Stand	0.17	0.3(0.2)	0.3(0.2)	0
				0.25		0.5(0.2)	+66.7
				0.33		1.0(0.5)	+233.3

CTRL= control subjects; QUAD= quadriplegic patients; CHF= congestive heart failure patients; HUT= head-up tilt; SR= spontaneous respiration; CR= controlled respiration; % Change= % change from spontaneous respiration.
Mean (SEM)

range (11.3-48.6%) when compared to spontaneous respiration. In addition, the LF/HF ratio decreased by an average of 44.4%, range (26.4-72.0%) in controls.

Two studies combined controlled respiration and orthostatic stress. Control subjects breathing at 0.17 and 0.25 Hz, had a greater effect of controlled respiration on the HF component in the standing than supine position. However, this was not found in congestive heart failure patients, who did not exhibit a systematic response to controlled respiration at either of these breathing rates. At higher imposed respiratory frequencies (0.33 Hz) in control subjects such as used by both Pagani et al. (1986) and Sanderson et al. (1996), controlled respiration with passive 90° HUT induced a greater increase in the HF component by 96.2% whereas in standing an increase of only 11.4% was observed.

These studies may be taken to demonstrate that during standing or passive HUT where sympathetic influences to the sinus node are enhanced and vagal influences minimized, controlled respiration can emphasize appearance of the heart rate variability in the respiratory or HF component of the heart rate spectrum.

There were only two studies with patient populations using controlled respiration. Guzzetti et al. (1994) studied quadriplegic patients with clinically complete spinal traumatic transection at the C_5-C_7 level. Their response to controlled respiration was more pronounced than controls. Quadriplegic patients showed a significantly greater HF component (66 ± 6 vs. 46 ± 4, nu) with controlled respiration ($p < 0.01$) and a reduced LF component (23 ± 7 vs. 44 ± 3, nu) ($p < 0.05$) than controls. Yet the relative change in the LF/HF ratio was similar in both groups (QUAD: -22.8 vs. CTRL: -26.4, %). In congestive heart failure patients the expected response to controlled respiration of an

increased HF component and a decreased LF component to controlled respiration was only observed when the respiratory rate was 0.17 Hz in the supine position. At higher breathing rates of 0.25 and 0.33 Hz regardless of body posture, the HF component decreased or remained unchanged and the LF component increased (Sanderson et al., 1996).

3.4 Effects of Passive Head-Up Tilt / Standing

Passive head-up tilt (HUT) or active tilt (standing) induces sympathetic excitation and vagal withdrawal. Tables 4A, 4B, and 4C summarize the effects of passive head-up tilt or standing on the HF and LF spectral power components and LF/HF ratio of HRV spectral analysis in control subjects and patient populations, respectively. Studies of control subjects in which HUT was used as an orthostatic stressor regardless of tilt angle and not developing syncope demonstrated that as expected, the HF component decreased by an average 58.0%, range (29.4-81.4%), the LF component increased by an average of 85.8%, range (31.2-238.4%), and the LF/HF ratio increased by 580.8%, range (177.6-1576.3%) from the supine position. The majority of patient populations showed similar responses. In patients, the HF component decreased by an average of 40.8%, range (13.7-68.4%), the LF component increased by an average of 41.1%, range (5.4-168.8%), and the LF/HF ratio increased by 245.8% range (15.6-672.7%). However, not all patient populations responded accordingly. Patients with or without a previous history of syncope and who had a positive tilt test demonstrated an increase in the HF spectral component as opposed to an observed decrease in their control counterparts. While there was an observed increase in the LF component in patients with a positive tilt test, it was either insufficient (38.5 vs. 167.2%) or exaggerated (144.0 vs. 38.5%) compared to

Table 4. Effect of head-up tilt or standing on spectral components of R-R variability in control subjects and patient populations.

A) High frequency component

Study	Subjects/N	Age (y)	Mode	Angle (°)	Duration (min)	HF Supine (nu)	HF HUT/Stand (nu)	% Change
Dixon et al. (1992)	CTRL/14	27.4(2.6)	Stand		10	43.7(22.4)[1]	23.8(11.4)[1]	-45.5
Furlan et al. (1993)	CTRL/29	16.0(0.4)	HUT	90	15	53.12(2.59)	21.54(1.92)	-59.4
Guzzetti et al. (1991)	CTRL/12	39(4)	Stand		15	44.2(4.2)	17.9(4.7)	-59.5
	CC(1)/7	40(4)				43.0(7.6)	40.9(12.7)	-4.9
	CC(2)/12	51(4)				51.6(6.0)	51.4(6.5)	-0.4
Guzzetti et al. (1994)	CTRL/15	34(3)	HUT	80	10	41(4)	11(2)	-73.2
	QUAD/6	33(4)	HUT	40	10	56(5)	69(9)	+23.2
Hartikainen et al. (1997)	CTRL/14	33.1(2.6)	HUT	60	10	51(4)	30(4)	-41.2
	AVNRT/17	36.8(3.4)				51(5)	28(3)	-45.1
	AVRT/14	35.0(3.4)				39(5)	23(3)	-41.0
Kamath et al. (1991)	CTRL/19	(20-32)	Stand		10	41.7(20.0)[1]	26.1(13.3)[1]	-37.4
Lipsitz et al. (1990)	CTRL/10	(71-94)	HUT	60	15	0.19(0.09)[2]	0.19(0.13)[2]	0
	CTRL/6	(18-35)				1.60(1.47)[2]	1.13(0.64)[2]	-29.4
	CTRL/6	(18-35)				0.95(0.28)[2]	1.08(0.83)[2]	+13.7
Lombardi et al. (1987)	CTRL/26	52(3)	HUT	90	20	35(3)	14(2)	-60.0
	MI(1)/24	54(2)				19(3)	13(2)	-31.6
	MI(2)/19					28(2)	11(2)	-60.7
Lombardi et al. (1992)	VA/8	NA	HUT	90	20	38(5)	12(2)	-68.4
Lucini et al. (1994)	N/63	31(2)	Stand		10	37(2)	13(2)	-64.9
	HYP/78	48(1)				31(2)	18(2)	-41.9
Montano et al. (1994)	CTRL/22	(22-66)	HUT	60	10	~47.2	~18.9	-60.0
				90	10		~8.8	-81.4
Morillo et al. (1994)	CTRL/15	34(12)	HUT	60	15	2.2(0.6)[3]	1.1(0.5)[3]	-50.0
	-HUT/15	33.5(13)				2.3(0.7)[3]	1.2(0.8)[3]	-47.8
	+HUT/15	32(14)				2.4(0.8)[3]	4.6(0.8)[3]	+91.7
Pagani et al. (1986)	CTRL/30	(20-30)	HUT	90	20	24.0(2.0)	7.5(0.9)	-68.8
	CTRL/10	(30-45)				26.3(4.3)	11.4(2.8)	-56.6
	CTRL/17	(45-60)				32.0(4.6)	16.2(3.4)	-49.4

Table 4A. Continued

Study	Subjects/N	Age (y)	Mode	Angle (°)	Duration (min)	HF Supine (nu)	HF HUT/Stand (nu)	% Change
Piccirillo et al. (1996)	N/9	38(13)	HUT	90	15	69.5(16.6)	33.1(18.5)	-52.4
	HYP/14	41(9)				30.7(13.7)	26.5(9.2)	-13.7
Pitzalis et al. (1996)	CTRL/18	28(2)	HUT	70	10	39.7(14.5)	20.9(11.3)	-47.4
Sanderson et al. (1996)	CTRL/9	45(2)	Stand		7	59.8(9.0)	22.7(9.6)	-62.0
	CHF/11	57(15)				63.7(5.4)	64.3(8.0)	+0.9
Thomaseth et al. (1990)	CTRL/10	36.1(6.7)	Stand		10	347(72)[2]	161(36)[2]	-53.6
	D/10	42.6(12.5)				12(2)[2]	7(1)[2]	-41.7
Veglio et al. (1995)	N/10	50.0(5.0)	HUT	60	10	32.0(2.6)	10.0(1.3)	-68.8
	EH/11	51.0(3.0)				22.7(4.5)	14.8(3.9)	-34.8
	IHA/10	52.0(3.7)				32.3(4.7)	20.7(4.8)	-35.9
	APA/7	51.5(3.9)				30.4(4.8)	21.6(5.0)	-28.9
Vybiral et al. (1989)	CTRL/17	29(7)	HUT	70	15	5205(3936)[2]	1475(1049)[2]	-71.7

CTRL= control subjects; CC(1)= chronic Chagas' disease patients with only positive serology; CC(2)= chronic Chagas' patients with positive serology and ECG abnormalities; QUAD= quadriplegic patients; AVNRT= atrioventricular nodal reentrant tachycardia patients; AVRT= orthodromic atrioventricular reentrant tachycardia patients; MI(1)= myocardial infarction patients at 2 weeks; MI(2)= myocardial infarction patients at 12 months; VA= ventricular arrhythmia patients; N= normotensive subjects; HYP= hypertensive subjects; -HUT= syncope patients with a negative tilt response; +HUT= syncope patients with a positive tilt response; CHF= congestive heart failure patients; D= diabetic patients; EH= essential hypertensive patients; IHA= idiopathic hyperaldosteronism patients; APA= aldosterone producing adenoma patients; NA= not available; HUT= head-up tilt; nu= normalized units; 1= $bpm^2 \bullet Hz^{-1}$; 2= arbitrary units; 3= ln bpm^2 ; % Change= % change from supine.
Mean (SEM)

Table 4. Effect of head-up tilt or standing on spectral components of R-R variability in control subjects and patient populations.

B) Low frequency component

Study	Subjects/N	Age (y)	Mode	Angle (°)	Duration (min)	LF Supine (nu)	LF HUT/Stand (nu)	% Change
Bootsma et al. (1994)	CTRL/21	25.3(4.1)	HUT	80	6	45.8(16.7)	79.8(13.8)	+74.2
Dixon et al. (1992)	CTRL/14	27.4(2.6)	Stand		10	69.6(19.5)[1]	82.9(17.6)[1]	+19.1
Furlan et al. (1993)	CTRL/29	16.0(0.4)	HUT	90	15	37.41(2.90)	71.68(2.68)	+91.6
Guzzetti et al. (1991)	CTRL/12	39(4)	Stand		15	49.1(5.7)	77.2(4.4)	+57.2
	CC(1)/7	40(4)				52.9(8.7)	51.6(13.8)	-2.5
	CC(2)/12	51(4)				37.1(7.1)	36.3(7.7)	-2.2
Guzzetti et al. (1994)	CTRL/15	34(3)	HUT	80	10	51(3)	84(2)	+64.7
	QUAD/6	33(4)	HUT	40	10	35(5)	17(11)	-51.4
Hartikainen et al. (1997)	CTRL/14	33.1(2.6)	HUT	60	10	49(4)	70(4)	+42.8
	AVNRT/17	36.8(3.4)				49(5)	72(3)	+46.9
	AVRT/14	35.0(3.4)				61(5)	77(3)	+26.2
Kamath et al. (1991)	CTRL/19	(20-32)	Stand		10	68.4(18.9)[1]	76.6(26.7)[1]	+12.0
Lipsitz et al. (1990)	CTRL/10	(71-94)	HUT	60	15	0.30(0.16)[2]	0.26(0.22)[2]	-13.3
	CTRL/6	(18-35)				1.51(1.03)[2]	2.05(1.74)[2]	+35.8
	CTRL/6	(18-35)				1.16(0.66)[2]	2.83(1.70)[2]	+144.0
Lombardi et al. (1987)	CTRL/26	52(3)	HUT	90	20	53(3)	78(3)	+47.2
	MI(1)/24	54(2)				74(3)	78(3)	+5.4
	MI(2)/19					53(3)	77(3)	+45.3
Lombardi et al. (1992)	VA/8	NA	HUT	90	20	53(5)	79(3)	+49.0
Lucini et al. (1994)	N/63	31(2)	Stand		10	53(2)	83(2)	+56.6
	HYP/78	48(1)				60(2)	74(2)	+23.3
Montano et al.. (1994)	CTRL/22	(22-66)	HUT	60	10	~34.4	~71.9	+109.0
				90	10		~85.9	+149.7
Morillo et al. (1994)	CTRL/15	34(12)	HUT	60	15	6.4(0.7)[3]	17.1(2.1)[3]	+167.2
	-HUT/15	33.5(13)				6.1(0.8)[3]	16.4(1.5)[3]	+168.8
	+HUT/15	32(14)				5.2(0.9)[3]	7.2(0.8)[3]	+38.5
Pagani et al. (1986)	CTRL/30	(20-30)	HUT	90	20	58.2(3.3)	89.7(1.4)	+54.1
	CTRL/10	(30-45)				62.2(6.3)	83.7(4.6)	+34.6
	CTRL/17	(45-60)				49.9(4.9)	75.7(4.6)	+51.7

Table 4B. Continued

Study	Subjects/N	Age (y)	Mode	Angle (°)	Duration (min)	LF Supine (nu)	LF HUT/Stand (nu)	% Change
Piccirillo et al. (1996)	N/9	38(13)	HUT	90	15	31.4(15.2)	66.9(18.5)	+113.0
	HYP/14	41(9)				69.3(13.7)	73.5(9.2)	+6.1
Pitzalis et al. (1996)	CTRL/18	28(2)	HUT	70	10	60.3(14.5)	79.1(11.3)	+31.2
Sanderson et al. (1996)	CTRL/9	45(2)	Stand		7	25.6(8.6)	59.3(10.5)	+131.6
	CHF/11	57(15)				12.5(5.4)	8.1(4.7)	-35.2
Thomaseth et al. (1990)	CTRL/10	36.1(6.7)	Stand		10	1024(218)^2	1190(187)^2	+16.2
	D/10	42.6(12.5)				18(8)^2	24(6)^2	+33.3
Veglio et al. (1995)	N/10	50.0(5.0)	HUT	60	10	49.0(2.6)	81.8(1.7)	+66.9
	EH/11	51.0(3.0)				69.5(5.4)	80.5(4.2)	+15.8
	IHA/10	52.0(3.7)				54.5(5.8)	69.3(6.0)	+27.2
	APA/7	51.5(3.9)				52.6(7.9)	63.3(11.0)	+20.3
Vybiral et al. (1989)	CTRL/17	29(7)	HUT	70	15	4755(3654)^2	16090(20527)^2	+238.4

CTRL= control subjects; CC(1)= chronic Chagas' disease patients with only positive serology; CC(2)= chronic Chagas' patients with positive serology and ECG abnormalities; QUAD= quadriplegic patients; AVNRT= atrioventricular nodal reentrant tachycardia patients; AVRT= orthodromic atrioventricular reentrant tachycardia patients; MI(1)= myocardial infarction patients at 2 weeks; MI(2)= myocardial infarction patients at 12 months; VA= ventricular arrhythmia patients; N= normotensive subjects; HYP= hypertensive subjects; -HUT= syncope patients with a negative tilt response; +HUT= syncope patients with a positive tilt response; CHF= congestive heart failure patients; D= diabetic patients; EH= essential hypertensive patients; IHA= idiopathic hyperaldosteronism patients; APA= aldosterone producing adenoma patients; NA= not available; HUT= head-up tilt; nu= normalized units; 1= $bpm^2 \bullet Hz^{-1}$; 2= arbitrary units; 3= ln bpm^2; % Change= % change from supine.
Mean (SEM)

Table 4. Effect of head-up tilt or standing on spectral components of R-R variability in control subjects and patient populations.

C) LF/HF ratio

Study	Subjects/N	Age (y)	Mode	Angle (°)	Duration (min)	LF/HF Supine	LF/HF HUT/Stand	% Change
Dixon et al. (1992)	CTRL/14	27.4(2.6)	Stand		10	1.60(0.85)	3.2(1.7)	+100.0
Furlan et al. (1993)	CTRL/29	16.0(0.4)	HUT	90	15	0.78(0.07)	4.54(0.59)	+482.0
Guzzetti et al. (1994)	CTRL/15	34(3)	HUT	80	10	1.55(0.25)	12.75(2.23)	+722.6
	QUAD/6	33(4)	HUT	40	10	0.70(0.14)	0.45(0.34)	-35.7
Hartikainen et al. (1997)	CTRL/14	33.1(2.6)	HUT	60	10	1.22(0.27)	3.47(0.73)	+184.4
	AVNRT/17	36.8(3.4)				1.35(0.29)	3.86(0.91)	+185.9
	AVRT/14	35.0(3.4)				3.26(1.27)	5.22(1.41)	+60.1
Kamath et al. (1991)	CTRL/19	(20-32)	Stand		10	2.1(1.2)	3.2(1.9)	+52.4
Lombardi et al. (1987)	CTRL/26	52(3)	HUT	90	20	2.0(0.3)	14.0(3.3)	+600.0
	MI(1)/24	54(2)				9.0(2.2)	13.0(2.3)	+44.4
	MI(2)/19					3.0(0.9)	14.0(3.3)	+366.7
Lombardi et al. (1992)	VA/8	NA	HUT	90	20	1.79(0.46)	11.9(5.0)	+564.8
Lucini et al. (1994)	N/63	31(2)	Stand		10	2(1)	14	+600.0
	HYP/78	48(1)				3(1)	8(1)	+166.7
Montano et al. (1994)	CTRL/22	(22-66)	HUT	60	10	~0.97	~9.39	+868.0
				90	10		~16.26	+1576.3
Morillo et al. (1994)	CTRL/15	34(12)	HUT	60	15	2.1(1.2)	18.8(3.4)	+795.2
	-HUT/15	33.5(13)				2.2(0.8)	17(3.1)	+672.7
	+HUT/15	32(14)				2.4(0.8)	1.6(3.5)	-33.3
Pagani et al. (1986)	CTRL/30	(20-30)	HUT	90	20	3.62(0.70)	20.79(3.68)	+474.3
	CTRL/10	(30-45)				3.69(1.23)	17.30(8.19)	+368.8
	CTRL/17	(45-60)				2.58(0.61)	12.61(3.21)	+388.6
Piccirillo et al. (1996)	N/9	38(13)	HUT	90	15	0.54(0.29)	2.94(2.16)	+444.4
	HYP/14	41(9)				3.2(2.6)	3.7(2.9)	+15.6
Pitzalis et al. (1996)	CTRL/18	28(2)	HUT	70	10	1.83(0.96)	5.08(3.43)	+177.6
Sanderson et al. (1996)	CTRL/9	45(2)	Stand		7	0.6(0.2)	4.7(0.3)	+683.3
	CHF/11	57(15)				0.3(0.1)	0.3(0.2)	0

Table 4C. Continued

Study	Subjects/N	Age (y)	Mode	Angle (°)	Duration (min)	LF/HF Supine	LF/HF HUT/Stand	% Change
Veglio et al. (1995)	N/10	50.0(5.0)	HUT	60	10	1.62(0.10)	9.2(1.2)	+467.9
	EH/11	51.0(3.0)				5.4(1.5)	10.0(2.4)	+85.2
	IHA/10	52.0(3.7)				2.1(0.4)	7.7(2.9)	+266.7
	APA/7	51.5(3.9)				2.03(0.50)	6.0(2.9)	+195.6

CTRL= control subjects: QUAD= quadriplegic patients; AVNRT= atrioventricular nodal reentrant tachycardia patients; AVRT= orthodromic atrioventricular reentrant tachycardia patients; MI(1)= myocardial infarction patients at 2 weeks; MI(2)= myocardial infarction patients at 12 months; VA= ventricular arrhythmia patients; N= normotensive subjects; HYP= hypertensive subjects; -HUT= syncope patients with a negative tilt response; +HUT= syncope patients with a positive tilt response; CHF= congestive heart failure patients; EH= essential hypertensive patients; IHA= idiopathic hyperaldosteronism patients; APA= aldosterone producing adenoma patients; NA= not available; HUT= head-up tilt; % Change= % change from supine.
Mean (SEM)

controls (Lipsitz et al., 1990; Morillo et al., 1994). Quadriplegic patients did not respond to 40° HUT as expected. The HF component increased by 23.2%, the LF component decreased by 51.4%, and the LF/HF ratio decreased by 35.7%. Thus, significant group differences were found for both spectral components and the LF/HF ratio ($p < 0.01$) (Guzzetti et al., 1994). Studies involving hypertensive patients indicated that although the response to HUT was in the same direction as normotensive subjects, the magnitude of change in both spectral components and the LF/HF ratio was attenuated (Piccirillo et al., 1996; Veglio et al., 1995). Both studies concluded that enhanced sympathetic activity in hypertensive patients at rest would explain the low capacity for increases in the LF component or LF/HF ratio following HUT. The results from a study by Lombardi et al. (1987) suggest that the longer the time following a myocardial infarction (MI), the better the response to 90° HUT. After only two weeks following a MI, patients had a 31.6% decrease in the HF component, an increase of only 5.4% in the LF component, and a 44.4% increase in the LF/HF ratio. Yet in patients with a longer period of time following a MI, 12 months, the percentage change of the HF, LF components and LF/HF ratio were similar to controls: a decrease in the HF component (60.7%, MI vs. 60.0%, controls), an increase in the LF component (45.3%, MI vs. 47.2%, controls), and an increase in the LF/HF ratio (366.7%, MI vs. 600.0%, controls). These results indicate that over a period of time following an MI, there is a recovery of vagal tone and a normalization of the LF/HF or sympatho-vagal interaction during resting conditions, as well as in response to HUT.

Studies have shown that age is correlated to both the LF and HF component and LF/HF ratio (Lipsitz et al., 1990; Pagani et al., 1986). In Lipsitz et al. (1990), control

subjects aged 71-94 years, failed to respond as expected to 60° HUT. The HF component did not change while the LF component decreased by 13.3%. As previously mentioned, this observation may be explained in part by at rest, with aging, there is an attenuation of respiratory sinus arrhythmia, thus a decrease in parasympathetic activity to the heart (Lipsitz et al., 1990; Shannon et al., 1987). Therefore, older subjects may be unable to withdraw vagal influence during HUT, since baseline values may be attenuated, explaining the lack of change in the HF component.

Tilt angle has also been demonstrated to affect the power spectral components of HRV and their respective ratio (Lipsitz et al., 1990; Pagani et al., 1986). When the angle of tilt was taken into consideration in control subjects who had a negative tilt test and divided into 2 groups, group (1) with studies using an angle between 60° and 70°, and group (2) with studies using an angle between 80° and 90°, the results were as follows: Controls decreased the HF component by 52.6 and 62.6%, increased the LF component by an average of 98.8 and 75.6%, and increased the LF/HF ratio by 498.6 and 632.1% in groups 1 and 2 respectively. These findings seem to indicate that an increase in tilt angle in control subjects as demonstrated by (Montano et al., 1994) show progressive decreases in the HF component, and increases in the LF component and LF/HF ratio.

An alternative method of achieving orthostatic stress is standing in the upright position after a supine period. This differs from passive HUT in that the muscles of the lower extremities and abdomen are used and exert a pumping influence on the blood vessels (Scott, 1995). The differences in initial hemodynamic response compared with HUT include a more abrupt increase in heart rate and initial systolic and diastolic blood

pressure trough followed by an overshoot (Dambrink et al., 1991; Dambrink & Weiling, 1987).

Studies using standing as an orthostatic stressor showed that control subjects decreased the HF component by 53.8%, range (37.4-64.9%), increased the LF component by an average of 48.8%, range (12.0-131.6%), and increased the LF/HF ratio by 358.9%, range (52.4-683.3%). Patients decreased the HF component by 22.2%, range (0.4-41.9%), increased the LF component by an average of 28.3%, range (23.3-33.3%), and increased the LF/HF ratio by 166.7%. However, both groups of patients with chronic Chagas' disease (CC) (a myocardial disease due to infection with the protozoan *Trypanosoma cruzi* and is associated with degenerative abnormalities that occur in various organs and tissues including the heart and the intrinsic cardiac innervation) (Koberle, 1968; Mott & Hagstrom, 1965) failed to respond as expected when changing from supine to a standing position. The HF component decreased but marginally at 4.9 and 0.4%, in CC(1) (patients with only positive serology) and CC(2) (patients with positive serology and associated electrocardiographic abnormalities) patients, respectively. In addition, the LF component in CC(1) and CC(2) patients decreased slightly by 2.5 and 2.2%, respectively (Guzzetti et al., 1991). Patients with congestive heart failure, also did not respond normally. The HF component increased slightly at 0.9%, the LF component decreased by 35.2%, and the LF/HF ratio did not change (Sanderson et al., 1996). As with passive HUT, hypertensive patients displayed a blunted decrease in the HF component and increase in the LF component and LF/HF ratio compared to their normotensive counterparts ($p < 0.05$) (Lucini et al., 1994).

When comparing 80-90° HUT to standing, the average relative changes in both spectral components and the LF/HF ratio of HRV from the supine position in control subjects were generally greater with HUT than standing (↓HF: 62.6 vs. 53.8%; ↑LF: 75.6 vs. 48.8%; ↑LF/HF: 632.1 vs. 358.9%). Similar patterns were observed in patients populations (↓HF: 43.6 vs. 22.2%; ↑LF: 26.4 vs. 28.3%; ↑LF/HF: 247.9 vs. 166.7%). In addition, when standing was used as orthostatic stressor in controls who had no previous history of syncope, no studies in tables 4A, 4B or 4C reported any premature termination of the test due to signs of syncope. However, there were occurrences of positive test results in controls where passive HUT was prematurely terminated due to syncopal symptoms (Bootsma et al., 1994; Furlan et al., 1993).

3.5 Heart Rate Variability during Dynamic Exercise

As in passive head-up tilt (HUT) or standing, dynamic exercise induces sympathetic excitation and vagal withdrawal leading to an overall fall in total heart rate variability (Bernardi et al., 1990; Casadei et al., 1995; Casadei et al., 1996; Lucini et al., 1995). Tables 5A, 5B and 5C summarize the effects of dynamic exercise of various intensities on the HF and LF power spectral components and LF/HF ratio respectively reported in some 12 studies conducted in the last 10 years in both healthy subjects as well as patient populations. While most studies concur to show an overall reduction in the HF component for low intensity exercise, comparisons and interpretation of results concerning spectral components is difficult due to differences in exercise intensity and protocols. In healthy subjects exercising at mild intensities for which heart rates between 100 and 115 bpm were reported, the decrease in total variance (in absolute units) ranged between 63 and 97% with an average of 83.5% compared to pre-exercise baseline values. Differences

Table 5. Effect of dynamic exercise on spectral components of R-R variability in control subjects and patient populations.

A) High frequency component

Study	Subjects/N	Age (y)	M	B	Int	HR (bpm)	HF Baseline (nu)	HF Exercise (nu)	% Change
Arai et al. (1989)	CTRL/43	(15-64)	C	Sit		103(2)	2.99(0.38)[1]	1.08(0.19)[1]	-63.9
						134(2)		0.36(0.04)[1]	-88.0
						160(3)		0.30(0.03)[1]	-90.0
	CHF/8	(20-75)				118(6)	0.15(0.03)[1]	0.27(0.03)[1]	+80.0
						127(6)		0.39(0.07)[1]	+160.0
						138(7)		0.34(0.05)[1]	+126.7
	HTX/6	(15-48)				103(5)	0.12(0.01)[1]	0.27(0.12)[1]	+125.0
						119(5)		0.45(0.11)[1]	+275.0
						137(10)		0.31(0.09)[1]	+158.3
Bernardi et al. (1990)	CTRL/9	23.1(0.7)	C	Sit	30W	105.2(3.5)	44.0(4.0)	37.0(6.3)	-15.9
					60W	122.4(4.2)		38.8(8.0)	-11.8
					90W	142.9(4.7)		71.7(11.8)	+63.0
					120W	160.4(5.0)		88.9(5.8)	+102.0
	HTX/6	48.3(3.1)			25W	107.1(3.8)	1.17(0.22)[2]	7.16(3.80)[2]	+512.0
					50W	122.0(4.1)		3.44(1.02)[2]	+194.0
Casadei et al. (1995)	CTRL/11	21.1(0.4)	C	Sit	110W	109.9	37.6(8.3)	~32.9	-12.5
					147W	126.1		~39.5	+5.0
					184W	141.5		~47.4	+26.1
					221W	154.8		80.4(5.3)	+113.8
Casadei et al. (1996)	CTRL/10	21(1)	C	Sup	25V	103.5	1693.0[2]	29.4[2]	-98.3
Dixon et al. (1992)	CTRL/14	27.4(2.6)	C	Up	50V	131(20.6)	23.8(11.4)[3]	21.8(10.3)[3]	-8.4
Hartikainen et al. (1997)	CTRL/14	33.1(2.6)	T	Up		106.9	27(4)	40(5)	+48.1
	AVNRT/17	36.8(3.4)				125.8	22(2)	55(7)	+150.0
	AVRT/14	35.0(3.4)				117.6	16(3)	37(7)	+131.2
Kamath et al. (1991)	CTRL/19	(20-32)	C	Up	50V	139.9(6.1)	26.1(13.3)[3]	21.8(10.2)[3]	-16.5
Lucini et al. (1995)	CTRL/15	32(9)	C	Sup	10V	87.1	38.4(14.3)	19.7(11.8)	-48.7
					20V	97.8		17.2(13.4)	-55.2
					30V	109.5		12.0(7.9)	-68.8
Perini et al. (1990)	CTRL/7	23.7(0.8)	C	Sit	21V	97.7	15.6(5.2)	~11.8	-24.4
					49V	128.2		~10.1	-35.2
					71V	150		~13.8	-11.5

Table 5A. Continued

Study	Subjects/N	Age (y)	M	B	Int	HR (bpm)	HF Baseline (nu)	HF Exercise (nu)	% Change
Radaelli et al. (1996)	CTRL/6		C	Sit	50W	82(4)	5.80(0.30)[4]	4.66(0.30)[4]	-19.6
					75W	93(6)		3.89(0.46)[4]	-32.9
					100W	106(7)		3.42(0.48)[4]	-41.0
					125W	120(9)		2.67(0.57)[4]	-54.0
					150W	136(9)		2.01(0.58)[4]	-65.3
	HTX/41	44			25sW	105(2)	1.45(0.16)[4]	2.00(0.17)[4]	+37.9
					25eW	109(2)		1.85(0.19)[4]	+27.6
					50W	120(3)		1.74(0.20)[4]	+20.0
					75W	132(3)		1.42(0.27)[4]	-2.1
Yamamoto et al. (1991)	CTRL/8	22(3)	C	Sit	20W	82	4230.16[2]	855.14[2]	-79.8
					30T	95		387.05[2]	-90.8
					60T	114		125.48[2]	-97.0
					90T	135		21.50[2]	-99.5
					100T	145		4.69[2]	-99.9
					110T	155		1.06[2]	-100.0

CTRL= control subjects; CHF= congestive heart failure patients; HTX= heart transplant patients; AVNRT= atrioventricular nodal reentrant tachycardia; AVRT= orthodromic atrioventricular reentrant tachycardia; M= mode of exercise: C= cycling; T= treadmill; B= baseline position; Sup= supine; Up= upright; Int= intensity of exercise: W= watts; V= % of maximum oxygen consumption; 25sW= 25 watts start (first 2 min); 25eW= 25 watts end (last 2 min); T= % ventilatory threshold; nu= normalized units; 1= bpm^2; 2= ms^2; 3= $bpm^2 \bullet Hz^{-1}$; 4= ln ms^2; % Change= % change from baseline values.
Mean (SEM)

Table 5. Effect of dynamic exercise on spectral components of R-R variability in control subjects and patient populations.

B) Low frequency component

Study	Subjects/N	Age (y)	M	B	Int	HR (bpm)	LF Baseline (nu)	LF Exercise (nu)	% Change
Arai et al. (1989)	CTRL/43	(15-64)	C	Sit		103(2)	12.0(1.8)[1]	4.47(0.54)[1]	-62.8
						134(2)		1.11(0.12)[1]	-90.8
						160(3)		0.65(0.10)[1]	-94.6
	CHF/8	(20-75)				118(6)	0.58(0.20)[1]	0.20(0.09)[1]	-65.5
						127(6)		0.13(0.04)[1]	-77.6
						138(7)		0.18(0.07)[1]	-69.0
	HTX/6	(15-48)				103(5)	0.23(0.17)[1]	0.10(0.04)[1]	-56.5
						119(5)		0.04(0.01)[1]	-82.6
						137(10)		0.23(0.11)[1]	0
Bernardi et al. (1990)	CTRL/9	23.1(0.7)	C	Sit	30W	105.2(3.5)	56.0(4.0)	63.0(6.3)	+12.5
					60W	122.4(4.2)		61.2(8.0)	+9.3
					90W	142.9(4.7)		28.3(11.8)	-49.5
					120W	160.4(5.0)		11.1(5.8)	-80.2
	HTX/6	48.3(3.1)			25W	107.1(3.8)	0[2]	0[2]	
					50W	122.0(4.1)		0[2]	
Casadei et al. (1995)	CTRL/11	21.1(0.4)	C	Sit	110W	109.9	53.1(8.0)	62.2(6.7)	+17.1
					147W	126.1		~50	-5.8
					184W	141.5		~34.2	-35.6
					221W	154.8		0	-100.0
Casadei et al. (1996)	CTRL/10	21(1)	C	Sup	25V	103.5	1736.6[2]	201.3[2]	-88.4
Dixon et al. (1992)	CTRL/14	27.4(2.6)	C	Up	50V	131(20.6)	82.9(17.6)[3]	67.6(21.6)[3]	-18.4
Hartikainen et al. (1997)	CTRL/14	33.1(2.6)	T	Up		106.9	73(4)	60(5)	-17.8
	AVNRT/17	36.8(3.4)				125.8	78(2)	45(7)	-42.3
	AVRT/14	35.0(3.4)				117.6	84(3)	62(7)	-26.2
Kamath et al. (1991)	CTRL/19	(20-32)	C	Up	50V	139.9(6.1)	76.6(26.7)[3]	55.2(18.8)[3]	-27.9
Lucini et al. (1995)	CTRL/15	32(9)	C	Sup	10V	87.1	54.1(20.2)	68.1(15.0)	+25.9
					20V	97.8		72.2(16.9)	+33.4
					30V	109.5		77.7(11.2)	+43.6
Perini et al. (1990)	CTRL/7	23.7(0.8)	C	Sit	21V	97.7	48.9(6.8)	~52.3	+7.0
					49V	128.2		~25.7	-47.4
					71V	150		~16.2	-66.9

Table 5B. Continued

Study	Subjects/N	Age (y)	M	B	Int	HR (bpm)	LF Baseline (nu)	LF Exercise (nu)	% Change
Radaelli et al. (1996)	CTRL/6		C	Sit	50W	82(4)	6.9(0.2)[4]	6.10(0.52)[4]	-11.6
					75W	93(6)		5.81(0.27)[4]	-15.8
					100W	106(7)		5.10(0.31)[4]	-26.1
					125W	120(9)		4.28(0.27)[4]	-38.0
					150W	136(9)		3.33(0.53)[4]	-51.7
	HTX/41	44			25sW	105(2)	--	--	
					25eW	109(2)	--	--	
					50W	120(3)	--	--	
					75W	132(3)	--	--	
Yamamoto et al. (1991)	CTRL/8	22(3)	C	Sit	20W	82	2285.73[2]	467.09[2]	-79.6
					30T	95		322.85[2]	-85.9
					60T	114		31.99[2]	-98.6
					90T	135		8.72[2]	-99.6
					100T	145		8.40[2]	-99.6
					110T	155		5.57[2]	-99.8

CTRL= control subjects; CHF= congestive heart failure patients; HTX= heart transplant patients; AVNRT= atrioventricular nodal reentrant tachycardia; AVRT= orthodromic atrioventricular reentrant tachycardia; M= mode of exercise; C= cycling; T= treadmill; B= baseline position; Sup= supine; Up= upright; Int= intensity of exercise; W= watts; V= % of maximum oxygen consumption; 25sW= 25 watts start (first 2 min); 25eW= 25 watts end (last 2 min); T= % ventilatory threshold; nu= normalized units; 1= bpm^2; 2= ms^2; 3= $bpm^2 \bullet Hz^{-1}$; 4= ln ms^2; % Change= % change from baseline values.
Mean (SEM)

Table 5. Effect of dynamic exercise on spectral components of R-R variability in control subjects and patient populations.

C) LF/HF ratio

Study	Subjects/N	Age (y)	M	B	Int	HR (bpm)	LF/HF Baseline	LF/HF Exercise	% Change
Arai et al. (1989)	CTRL/43	(15-64)	C	Sit		103(2)	4.8(0.5)	6.7(1.0)	+39.6
						134(2)		3.7(0.5)	-22.9
						160(3)		2.6(0.4)	-45.8
	CHF/8	(20-75)				118(6)	5.3(2.7)	1.2(0.8)	-77.4
						127(6)		0.7(0.4)	-86.8
						138(7)		0.5(0.1)	-90.6
	HTX/6	(15-48)				103(5)	1.5(0.9)	0.5(0.2)	-66.7
						119(5)		0.1(0.1)	-93.3
						137(10)		0.9(0.3)	-40.0
Casadei et al. (1996)	CTRL/10	21(1)	C	Sup	25V	103.5	1.90(0.63)	7.72(2.13)	+306.3
Dixon et al. (1992)	CTRL/14	27.4(2.6)	C	Up	50V	131(20.6)	3.2(1.7)	3.2(1.6)	0
Hartikainen et al. (1997)	CTRL/14	33.1(2.6)	T	Up		106.9	4.16(0.78)	2.14(0.45)	-48.6
	AVNRT/17	36.8(3.4)				125.8	4.60(0.71)	1.83(0.73)	-60.2
	AVRT/14	35.0(3.4)				117.6	7.28(1.39)	3.58(1.37)	-50.8
Kamath et al. (1991)	CTRL/19	(20-32)	C	Up	50V	139.9(6.1)	3.2(1.9)	3.6(2.5)	+12.5
Lucini et al. (1995)	CTRL/15	32(9)	C	Sup	10V	87.1	1.9(1.4)	6.5(7.2)	+242.1
					20V	97.8		8.2(6.9)	+331.6
					30V	109.5		10.6(8.9)	+457.9
Perini et al. (1990)	CTRL/7	23.7(0.8)	C	Sit	21V	97.7	7.6(2.7)	~5.6	-26.3
					49V	128.2		~4	-47.4
					71V	150		~4.4	-42.1
Radaelli et al. (1996)	CTRL/6		C	Sit	50W	82(4)	3.95(1.16)	5.04(1.24)	+27.6
					75W	93(6)		5.71(2.20)	+44.6
					100W	106(7)		7.33(3.91)	+85.6
					125W	120(9)		7.31(3.65)	+85.1
					150W	136(9)		4.35(2.59)	+10.1
Yamamoto et al. (1991)	CTRL/8	22(3)	C	Sit	20W	82	0.58(0.26)	1.68(0.59)	+189.6
					30T	95		1.58(0.70)	+172.4
					60T	114		0.85(0.49)	+46.6
					90T	135		1.20(0.55)	+106.9
					100T	145		1.77(0.46)	+205.2
					110T	155		6.19(1.70)	+967.2

CTRL= control subjects; CHF= congestive heart failure patients; HTX= heart transplant patients; AVNRT= atrioventricular nodal reentrant tachycardia; AVRT= orthodromic atrioventricular reentrant tachycardia; M= mode of exercise; C= cycling; T= treadmill; B= baseline position; Sup= supine; Up= upright; Int= intensity of exercise; W= watts; V= % of maximum oxygen consumption; T= % ventilatory threshold; % Change= % change from baseline values.
Mean (SEM)

in body position may account for some of the dispersion in the extent of vagal withdrawal (Perini et al., 1993). Decomposition of the heart rate variability spectrum for such exercise intensities indicate healthy subjects to show a significant decrease in the magnitude of the HF spectral power component by an average of 52.7%, range (12.5-98.3%), while average increases of 20% (7.0-43.6%) and 187.2%(39.6-457.9%) were found for the LF component and the LF/HF ratio respectively. While most studies report the fall in HF component to be significant (Casadei et al., 1995; Casadei et al., 1996; Lucini et al., 1995; Radaelli et al., 1996) the increase in the LF component or in the LF/HF ratio has at times been seen to be non-significant (Bernardi et al., 1990; Casadei et al., 1995) or marginally significant (Lucini et al., 1995).

With moderate exercise intensities, defined here as steady state heart rates between 125 and 145 bpm, healthy subjects showed the total variance in absolute units to decrease by an average of 92.3% compared to pre-exercise values suggesting a progressive change related to exercise intensity. Observations on spectral components show concurrent decreases in both the LF and HF spectral power component in absolute units. However, when expressed in normalized units, the HF vagally-mediated power component may be seen to increase on account of ventilatory changes (Bernardi et al., 1990; Casadei et al., 1995). Results from a recent exercise study following trimetaphan camsylate administration to block endogenous transmission to cholinergic ganglions indicate that as vagal tone decreases with exercise, an increasing proportion of respiratory sinus arrhythmia (RSA) is due to non-neural mechanisms (Casadei et al.,1996). The data showed that during mild exercise (25% of peak oxygen uptake) non-neural mechanism related to breathing accounted for approximately one-third of the amplitude of RSA. The

increasing contribution of non-neuronal ventilatory influences expressed by the HF component in normalized units leads to an inevitable decrease in the resulting LF spectral component or the LF/HF ratio (Tables 5A, 5B, 5C).

Few studies have used heart rate variability during dynamic exercise in patient populations. Data from heart transplant recipients (Arai et al., 1989; Bernardi et al., 1990; Radaelli et al., 1996) taken during steady-state exercising heart rates below 120 bpm indicated the HF component to increase by magnitudes 125, 512 and 38% respectively from pre-exercise values. This observation which is in opposite direction to that observed in their control counterparts may be taken to confirm the involvement of the respiratory non-neural mechanism in the behavior of the HF component during exercise. Patients with severe congestive heart failure also showed an increase in the HF spectral power component during exercise (Arai et al., 1989) although comparison between heart transplant and congestive heart failure patients is difficult on account of the differences in resting and/or exercising heart rates. A possible explanation for this increase in the HF spectral power component may be that the total variance at rest in heart transplant recipients or congestive heart failure patients is already very low and during exercise it remains unchanged (Arai et al., 1989; Radaelli et al., 1996) or actually increases (Bernardi et al., 1990).

Conflicting results with exercise in addition to intensity level may also be contributed to methodological considerations such as units being used. When spectral power is expressed in absolute units such as ms^2 or bpm^2, the results show a fall in absolute heart rate variability (Arai et al., 1989; Casadei et al., 1996; Dixon et al., 1992; Kamath et al., 1991; Radaelli et al., 1996; Yamamoto et al., 1991). However, the use of

absolute units (ms^2 or bpm^2) does not provide any indication of the relative contributions of the HF or LF modulatory influences to the total variation in heart rate. Normalized units on the other hand, provide a correction for the drastic reduction in total power that occurs with exercise, while still allowing an accurate determination of the relative distribution of the spectral power within the HF and LF bands (Malik et al., 1996).

Discrepancies in the HF and LF responses to exercise may also be contributed to different exercise protocols and failure to achieve appropriate steady-state heart rate conditions (Casadei et al., 1995). Autonomic adjustments to exercise depend strongly on the type of muscular activity, the intensity of the effort, its duration and the size of the muscle mass involved. In addition, in some studies the influence of autonomic adjustment to changes in posture, i.e., baseline measurements were taken in the upright position and exercise was performed in the sitting position (Dixon et al., 1992; Kamath et al., 1991) may confound the interpretation of the magnitude of the response to exercise.

3.6 Response during Recovery

Heart rate variability analysis has also been assessed at various stages of recovery following cessation of exercise. In general, total variance gradually returns towards pre-exercise values upon cessation. The extent of change in total variance appears to be largely dependent on the final exercise intensity and post-exercise recovery time. Tables 6A, 6B and 6C summarize the effects of recovery following exercise on the HF and LF spectral components and LF/HF ratio in control subjects and patient populations respectively. The expected response following the cessation of exercise would be the reappearance of vagal activity. Since there were conflicting results with exercise, interpretation of recovery data may be difficult. Although most studies demonstrate a relative increase in the HF component when expressed in absolute units following exercise in controls (Arai et al., 1989; Dixon et al., 1992; Kamath et al., 1991; Radaelli et al., 1996), others expressing the HF component in normalized units report a decrease compared to the last exercise bout (Bernardi et al., 1990; Hartikainen et al., 1997; Perini et al., 1990). This may be related to relative loss of the non-neural ventilatory component after cessation of exercise. Heart transplant recipients showed a relative decrease in the HF component after 8 minutes of recovery following a workload of 50-80 Watts which may perhaps be due to a decrease in respiratory rate and thus RSA after exercise (Arai et al., 1989; Bernardi et al., 1990; Radaelli et al., 1996) (Table 6A). The majority of studies showed a relative percentage increase in the LF component in post-exercise values in both controls and patient populations (Table 6B). All but one study (Dixon et al., 1992) showed an increase in the LF/HF ratio in controls (Table 6C).

Table 6. Effect of recovery following cessation of exercise on spectral components of R-R variability in control subjects and patient populations.

A) High frequency component

Study	Subjects/N	Age (y)	Final Exercise Intensity	Post-Ex time (min)	HF Exercise (nu)	HF Recovery (nu)	% Change
Arai et al. (1989)	CTRL/43	(15-64)	160(3) bpm	1-2	0.30(0.03)[1]	1.21(0.14)[1]	+303.3
				4-5		0.66(0.10)[1]	+120.0
				8-9		0.96(0.19)[1]	+220.0
	CHF/8	(20-75)	70W	1-2	0.34(0.05)[1]	0.34(0.06)[1]	0
				4-5		0.24(0.07)[1]	-29.4
				8-9		0.25(0.09)[1]	-26.5
	HTX/6	(15-48)	80W	1-2	0.31(0.09)[1]	0.79(0.40)[1]	+154.8
				4-5		0.31(0.15)[1]	0
				8-9		0.15(0.05)[1]	-51.6
Bernardi et al. (1990)	CTRL/9	23.1(0.7)	120W	4	88.9(5.8)	31.7(9.1)	-64.3
				8		20.7(2.3)	-76.7
	HTX/6	48.3(3.1)	50W	4	3.44(1.02)[2]	0.87(0.29)[2]	-74.7
				8		0.90(0.25)[2]	-73.8
Dixon et al. (1992)	CTRL/14	27.4(2.6)	50V	5	21.8(10.3)[3]	35.8(30.7)[3]	+64.2
				10		29.7(13.6)[3]	+36.2
				15		34.8(15.9)[3]	+59.6
Hartikainen et al. (1997)	CTRL/14	33.1(2.6)	100-130 bpm	2-5	40(5)	22(4)	-45.0
	AVNRT/17	36.8(3.4)		2-5	55(7)	20(4)	-63.6
	AVRT/14	35.0(3.4)		2-5	38(7)	19(4)	-50.0
Kamath et al. (1991)	CTRL/19	(20-32)	50V	5	21.8(10.2)[3]	22.6(10.9)[3]	+3.7
				10		28.1(14.3)[3]	+28.9
				15		31.0(18.0)[3]	+42.2
Perini et al. (1990)	CTRL/7	23.7(0.8)	21V	5	~11.8	~9.9	-16.1
			49V	5	~10.1	~7.9	-21.8
			71V	5	~13.8	~5.3	-61.6
Radaelli et al. (1996)	CTRL/6		150W	10	2.01(0.58)[4]	2.81(0.45)[4]	+39.8
	HTX/41	44	75W		1.42(0.27)[4]	0.97(0.23)[4]	-31.7

CTRL= control subjects; CHF= congestive heart failure patients; HTX= heart transplant patients; AVNRT= atrioventricular nodal reentrant tachycardia; AVRT= orthodromic atrioventricular reentrant tachycardia; W= watts; V= % of maximum oxygen consumption; nu= normalized units; 1= bpm^2; 2= ms^2; 3= $bpm^2 \cdot Hz^{-1}$; 4= ln ms^2; % Change= % change from exercise values.
Mean (SEM)

Table 6. Effect of recovery following cessation of exercise on spectral components of R-R variability in control subjects and patient populations.

B) Low frequency component

Study	Subjects/N	Age (y)	Final Exercise Intensity	Post-Ex time (min)	LF Exercise (nu)	LF Recovery (nu)	% Change
Arai et al. (1989)	CTRL/43	(15-64)	160(3) bpm	1-2	0.65(0.10)[1]	7.55(1.00)[1]	+1061.5
				4-5		3.96(0.57)[1]	+509.2
				8-9		7.66(1.07)[1]	+1078.5
	CHF/8	(20-75)	70W	1-2	0.18(0.07)[1]	0.79(0.20)[1]	+338.9
				4-5		0.62(0.33)[1]	+244.4
				8-9		0.56(0.15)[1]	+211.1
	HTX/6	(15-48)	80W	1-2	0.23(0.11)[1]	0.16(0.10)[1]	-30.4
				4-5		0.07(0.03)[1]	-69.6
				8-9		0.14(0.06)[1]	-39.1
Bernardi et al. (1990)	CTRL/9	23.1(0.7)	120W	4	11.1(5.8)	68.2(9.1)	+514.4
				8		79.3(2.3)	+614.4
	HTX/6	48.3(3.1)	50W	4	0[2]	0[2]	
				8		0[2]	
Dixon et al. (1992)	CTRL/14	27.4(2.6)	50V	5	67.6(21.6)[3]	69.9(27.7)[3]	+3.4
				10		81.5(25.4)[3]	+20.6
				15		85.5(26.4)[3]	+26.5
Hartikainen et al. (1997)	CTRL/14	33.1(2.6)	100-130 bpm	2-5	60(5)	78(4)	+30.0
	AVNRT/17	36.8(3.4)		2-5	45(7)	80(7)	+77.8
	AVRT/14	35.0(3.4)		2-5	62(7)	81(4)	+30.6
Kamath et al. (1991)	CTRL/19	(20-32)	50V	5	55.2(18.8)[3]	72.3(28.7)[3]	+31.0
				10		69.2(32.3)[3]	+25.4
				15		74.3(22.0)[3]	+34.6
Perini et al. (1990)	CTRL/7	23.7(0.8)	21V	5	~52.3	~55.3	+5.7
			49V	5	~25.7	~59.3	+130 7
			71V	5	~16.2	~53.3	+229.0
Radaelli et al. (1996)	CTRL/6		150W	10	3.33(0.53)[4]	4.54(0.52)[4]	+36.3
	HTX/41	44	75W		--	--	

CTRL= control subjects; CHF= congestive heart failure patients; HTX= heart transplant patients; AVNRT= atrioventricular nodal reentrant tachycardia; AVRT= orthodromic atrioventricular reentrant tachycardia; W= watts; V= % of maximum oxygen consumption; nu= normalized units; 1= bpm^2; 2= ms^2; 3= $bpm^2 \bullet Hz^{-1}$; 4= ln ms^2; % Change= % change from exercise values.
Mean (SEM)

Table 6. Effect of recovery following cessation of exercise on spectral components of R-R variability in control subjects and patient populations.

C) LF/HF ratio

Study	Subjects/N	Age (y)	Final Exercise Intensity	Post-Ex time (min)	LF/HF Exercise	LF/HF Recovery	% Change
Arai et al. (1989)	CTRL/43	(15-64)	160(3) bpm	1-2	2.6(0.4)	8.7(1.5)	+234.6
				4-5		6.8(0.7)	+161.5
				8-9		11.1(1.4)	+326.9
	CHF/8	(20-75)	70W	1-2	0.5(0.1)	2.7(0.8)	+440.0
				4-5		2.3(0.5)	+360.0
				8-9		3.6(1.3)	+620.0
	HTX/6	(15-48)	80W	1-2	0.9(0.3)	0.1(0.1)	-88.9
				4-5		0.4(0.2)	-55.6
				8-9		0.8(0.3)	-11.1
Dixon et al. (1992)	CTRL/14	27.4(2.6)	50V	5	3.2(1.6)	2.9(1.8)	-9.4
				10		2.9(1.9)	-9.4
				15		2.4(1.2)	-25.0
Hartikainen et al. (1997)	CTRL/14	33.1(2.6)	100-130 bpm	2-5	2.14(0.45)	5.72(0.91)	+167.3
	AVNRT/17	36.8(3.4)		2-5	1.83(0.73)	5.25(0.85)	+186.9
	AVRT/14	35.0(3.4)		2-5	3.58(1.37)	7.49(1.88)	+109.2
Kamath et al. (1991)	CTRL/19	(20-32)	50V	5	3.6(2.5)	4.1(2.5)	+13.9
				10		3.9(2.9)	+8.3
				15		3.5(2.6)	-2.8
Perini et al. (1990)	CTRL/7	23.7(0.8)	21V	5	~5.6	~7.1	+26.8
			49V	5	~4	~9.6	+140.0
			71V	5	~4.4	~17.8	+304.5
Radaelli et al. (1996)	CTRL/6		150W	10	4.35(2.59)	12.63(7.49)	+190.3
	HTX/41	44	75W		--	--	

CTRL= control subjects; CHF= congestive heart failure patients; HTX= heart transplant patients; AVNRT= atrioventricular nodal reentrant tachycardia; AVRT= orthodromic atrioventricular reentrant tachycardia; W= watts; V= % of maximum oxygen consumption; % Change= % change from exercise values.
Mean (SEM)

When post-exercise recovery values in control subjects were compared to pre-exercise baseline values, studies which had final exercise intensities that achieved steady-state heart rate below 140 bpm generally showed HF spectral power component values to have returned to pre-exercise values after 10 minutes of passive recovery (Dixon et al., 1992; Hartikainen et al., 1997; Kamath et al., 1991). However, in two of these studies (Dixon et al., 1992; Kamath et al., 1991) since exercise was performed in the seated position and subjects were in the supine position during recovery there may exist a confounding influence of body posture resulting in an enhanced vagal component. In studies where the final exercise intensity attained heart rates of 160 bpm (Arai et al., 1989; Bernardi et al., 1990), HF values were still lower than pre-exercise values indicating that the higher the final intensity, the longer period of time needed for re-establishing pre-exercise baseline HF vagal values.

4.0 Conclusion

Over the last decade, analysis of heart rate variability has become a valuable tool in the assessment and prognosis of several diseases involving the autonomic nervous system. Respiratory sinus arrhythmia is the primary factor explaining resting heart rate variability and may be related to respiratory parasympathetic modulatory influences on the sinus node. The parasympathetic influence on heart rate variability may be enhanced using rhythmic breathing at a given rate to minimize spectral power dispersion. Thus, the extent of change in the respiratory or high frequency component of spectral heart rate variability may be taken as an index of parasympathetic responsiveness. Alternately, tilting or standing provide orthostatic challenges enabling investigation of the

low frequency modulations on heart rate variability which may be seen to result primarily although not exclusively from sympathetic influences. While total heart rate variability is known to decrease in response to dynamic exercise, comparison of the high and low frequency spectral component distributions in subjects exercising at a given exercise intensity may provide insight as to the extent of vagal withdrawal or sympathetic influences. Overall, the use of heart rate variability during these manoeuvres may thus be taken as a reflection of the integrity of the autonomic nervous system at the SA node.

While heart rate variability has been extensively studied in patients with coronary heart disease and/or congestive heart failure, there is to date little information regarding patients operated in early childhood for a congenital heart defect. Use of this technique may help us better understand the long-term physiological consequences of these defects or of their surgical correction on cardiovascular regulation.

5.0 Position of the Problem

There is to date little information regarding cardiovascular regulatory function in patients operated in early childhood for a congenital heart defect despite reports of an increased incidence of ventricular arrhythmia and a maximal exercise chronotropic limitation in these patients. Spectral analysis of heart rate variability presents the advantage of being a non-invasive technique that provides a qualitative assessment of sympathovagal balance as well as autonomic responsiveness to manoeuvres modulating parasympathetic and/or sympathetic influences on the SA node.

Post-operative medium-term studies of patients operated for tetralogy of Fallot in early childhood generally find these adolescents or young adults to enjoy a normal and

symptom-free life. An abnormal chronotropic response to maximal exercise is a common finding following surgical repair, patients showing maximal heart rate 10-20 beats/minute lower than those of age-matched healthy control subjects. The abnormality in heart rate response has generally been attributed to autonomic dysfunction although this question has not been specifically addressed.

The object of the present investigation was thus to compare heart rate variability of adolescents successfully operated for tetralogy of Fallot in early childhood to that of age-matched healthy control subjects in an attempt to assess sinus node function. Parasympathetic and sympathetic responsiveness of the SA node was examined using controlled breathing, tilting and steady state exercise manoeuvres.

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PART II: EXPERIMENTAL STUDY

Heart Rate and Blood Pressure Variability in Response to Controlled Respiration, Head-Up Tilt and Dynamic Submaximal Exercise in Patients Operated for Tetralogy of Fallot.

Post-operative medium-term studies of patients operated for tetralogy of Fallot (TOF) in early childhood generally find these adolescents or young adults to enjoy a normal and symptom-free life (Perry & Garson, 1995). An abnormal chronotropic response to maximal exercise is a common finding following surgical repair, patients showing maximal heart rate 10-20 beats/minute lower than those of age-matched healthy control subjects (Bouhour et al., 1984; Carvalho et al., 1992; Guillaumont et al., 1996; Lambert et al., 1980; Marx et al., 1988; Perrault et al., 1989; Takahashi et al., 1986; Tomassoni et al., 1991). The abnormality in heart rate response has generally been attributed to autonomic dysfunction (Driscoll et al., 1987) although this question has not been specifically addressed.

Modern signal processing techniques have enabled the application of mathematical procedures to investigate non-invasive beat-to-beat fluctuations of hemodynamic variables such as heart rate and blood pressure in an attempt to qualitatively if not quantitatively assess sympathovagal balance. Briefly, electrocardiographic signals are continuously recorded for determination of R-R intervals. After equidistant time samples are obtained power spectral analysis is performed using a Fast Fourier Transform procedure. The results produce a power spectrum, with two main frequency peaks: a high frequency or respiratory component (HF) representing parasympathetic efferent activity on the sinus node and a low frequency (LF) component reflecting both sympathetic and parasympathetic influences. The power of the HF spectral component may thus be considered an assessment of vagal influence while the ratio of LF to HF may be used as an

index of sympathovagal balance (Akselrod et al., 1981; Pagani et al., 1986; Pomeranz et al., 1985).

There exists very limited data on heart rate variability in patients with congenital heart defects. In one of only two reports published to date, Finley et al. (1989) examined heart rate variability during 10-15 minute recordings in both the supine and standing positions in young patients prior to and 5 months following surgical repair of atrial septal defect. Results showed patients to have lower total variability and HF spectral power compared to their age-matched healthy counterparts, yet post-operative heart rate variability was increased compared to pre-operative findings. It is interesting that similar to that found in subjects operated for TOF, patients operated for atrial septal defect in good clinical status also exhibit an abnormally low maximal heart rate (Perrault et al., 1992) . In the other study, Gordon et al. (1988) obtained continuous recordings over a mean period of 9 hours immediately following corrective surgery for a variety of congenital heart diseases. Patients were divided into those with uncomplicated postoperative clinical courses and those who had sustained cardiac arrest. Results indicated patients from the latter group to have spectral patterns significantly different from the other patient group. The LF/HF ratio found in patients with uncomplicated clinical courses ranged between 1.17 and 23.30, with values for patients operated for TOF (2) and ventricular and atrial septal defect (1) being, 3.43, 5.20 and 4.10 respectively. There exists however no data on heart rate variability in the long-term clinical course of patients operated for TOF.

This study was thus designed to describe sympathetic and parasympathetic influences on the sinus node using heart rate variability in patients operated for tetralogy

of Fallot. Responses to orthostatic challenges as well as mild exercise were compared to those of healthy age and sex matched control subjects.

METHODOLOGY

Subjects

Nine young adults aged 16.9 ± 1.08 years (range 11.9 to 22.7 years) who had undergone surgery for correction of tetralogy of Fallot in early childhood and eight healthy age and sex-matched control subjects were studied. Exclusion criteria for TOF patients included: moderate to severe pulmonary insufficiency, right ventricular to main or peripheral pulmonary artery gradient > 20 mmHg, residual ventricular septal defect, and the presence of arrhythmia. Table 1 summarizes anthropometric characteristics and baseline circulatory data of TOF patients and controls. The age at operation for TOF patients was (mean ± SEM) 3.8 ± 0.34 years (range, 2.6 to 5.8 years), and the follow-up period from surgery was 13.0 ± 1.12 years (range, 8.5 to 19.8 years). Three out of the nine patients had total cardiac repair as the primary treatment. The remaining six patients had had a previous Blalock-Taussig shunt. Total repair had been performed through right ventriculotomy in all patients. Electrocardiographic assessment revealed all patients to have regular resting sinus rhythm. Complete right bundle branch block was found in 4 patients while partial right bundle branch block was found in 4 patients. Patients were all well and leading normal lives with no overt symptoms of reduced exercise tolerance.

All subjects were normotensive and were not taking any medication. Subjects were instructed to avoid caffeinated and alcoholic beverages and to refrain from moderate, heavy or sustained exercise for a period of 12 hours prior to testing. In addition, they were informed to eat a light breakfast or lunch preceding the protocol. Written informed

Table 1. Anthropometric and baseline circulatory data of tetralogy of Fallot patients and control subjects.

Parameters	TOF (n = 9)	CTRL (n = 8)	p Value
Anthropometric data			
M/F	3 / 6	3 / 5	NS
Age (y)	16.9 (1.08)	19.0 (1.11)	NS
Height (m)	1.6 (0.01)	1.6 (0.03)	NS
Weight (kg)	61.0 (2.50)	58.4 (3.66)	NS
Body surface area (m^2)	2.7 (0.05)	2.7 (0.09)	NS
Body mass index (kg/m^2)	22.4 (1.07)	21.3 (0.97)	NS
Resting Physiologic data			
Heart rate (bpm)	70.6 (3.98)	63.7 (2.84)	NS
R-R interval (ms)	872.1 (49.39)	955.4 (42.03)	NS
Systolic BP (mmHg)	106.2 (2.88)	109.8 (5.17)	NS
Diastolic BP (mmHg)	66.9 (2.79)	68.8 (2.85)	NS

M indicates males; F, females; bpm, beats per minute; TOF= tetralogy of Fallot patients; CTRL= control subjects. Values are given as mean (SEM).

consent was obtained from all participants (in 1 patient parental consent was required). The investigation protocol was approved by the Ethics Committee of McGill University, Faculty of Education as well as both medical ethics committees of Ste.Justine's and Sacré-Coeur Hospitals.

Experimental Protocol and Instrumentation

Experiments were performed between 8:00 AM to 11:30 AM or at 1:00 PM to 4:30 PM in a quiet dimly lit room at comfortable room temperature (22-24° C). Subjects were asked to remain awake and relaxed throughout the testing procedures. They were adequately secured by around the shoulders and waist to an electrically driven tilt table to prevent them from falling during the tilt manoeuvre. Subjects were equipped with five adhesive electrocardiogram (ECG) electrodes firmly attached to the anterior chest. Care was taken to ensure that a prominent R wave was obtained for data processing, while avoiding any movement artefact. A continuous analogue signal of the ECG (modified lead III), of respiratory oscillations (obtained by a thermistor probe placed subjacent to the nares) and of beat-to-beat arterial blood pressure measured by finger photoplethysmography (Ohmeda Finapres, model 2300) were obtained. Blood pressure was also taken by conventional sphygmomanometry after each condition.

A baseline recording under quiet spontaneous breathing conditions was obtained after a 20-minute rest in the supine position followed by further recordings in each of the following conditions: supine quiet rest with a breathing rate set at 12 breaths/min (0.2 Hz) (controlled respiration); passive head-up tilt at 85° after a 10 minute adjustment period; quiet rest in the seated position under spontaneous breathing; quiet seated rest with

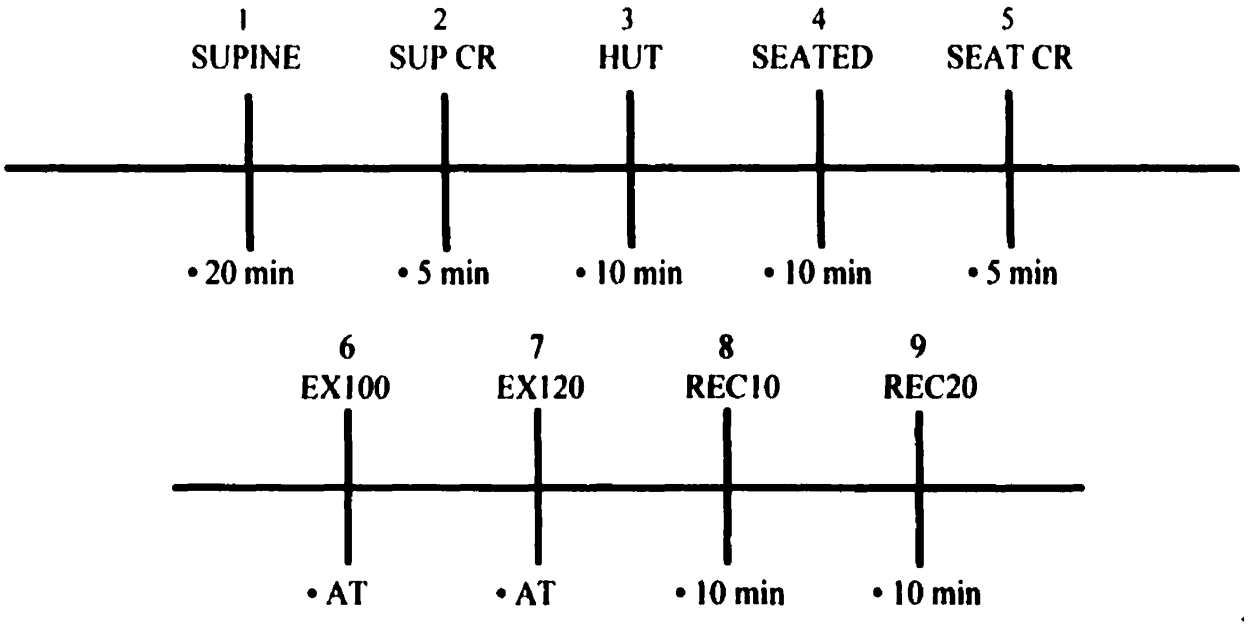
with controlled breathing rate set at 12 breaths/min (0.2 Hz); cycling at a pedalling rate of 70 rev/min at a steady-state heart rate of 100 bpm; cycling at a pedalling rate of 70 rev/min at a steady-state heart rate of 120 bpm; during seated recovery from exercise, 10 minutes following cessation of exercise; and during seated recovery from exercise, 20 minutes following cessation of exercise (Figure 1). For the exercise conditions, the pedalling resistance was adjusted in order to obtain steady state heart rates which were satisfied only when variations in heart rate readings were less than 5 bpm prior to initiating recording. The duration of recordings was adjusted to the steady-state heart rate in order to obtain a minimum of 532 R-R intervals under all conditions.

Data Acquisition and Analysis

Electrocardiogram, respiratory wave form and beat-to-beat finger blood pressure signals were recorded and stored on a PC-based system equipped with an eight channel analog to digital acquisition card (Data Translation model DT 2801). Satisfactory blood pressure recordings were obtained in all conditions except during exercise and exercise recovery conditions for which recordings could not be processed. Continuous data acquisition at a sampling rate of 250 Hz was achieved throughout the entire protocol.

The surface electrocardiogram was closely examined by the same investigator to ensure detection of the QRS complex appropriately followed atrial depolarization. Series of 532 consecutive R-R intervals were obtained and mean and standard deviation of the R-R intervals were calculated from the resulting tachogram. Respiration, R-R intervals, systolic and diastolic pressure values were linearly interpolated at 0.8 second intervals, since the equidistant data sampling of all time series is further required for spectral

Figure 1. Timeline of design protocol.



1. supine quiet rest position
2. supine position with controlled respiration set at 12 breaths/min (0.2 Hz)
3. passive head-up tilt at 85°
4. seated rest position
5. seated position with controlled respiration set at 12 breaths/min (0.2 Hz)
6. seated cycling set at 70 rev/min, to attain a steady-state of 100 bpm
7. seated cycling set at 70 rev/min, to attain a steady-state of 120 bpm
8. recovery 10 - 10 min post-exercise
9. recovery 20 - 20 min post-exercise

Note: For each condition, an appropriate amount of time was alloted for adaptational purposes to attain steady-state recordings; • = duration of adaptation period; AT = appropriate time. The time needed for each recording was conservatively estimated, to obtain a minimum of 532 beats (for power spectral analysis).

estimation. Time series were detrended by a fourth order moving polynomial to remove the baseline trends from all signals, which includes the very low non-stationary frequency below 0.005 Hz (Lepicovska et al., 1992).

A Fast Fourier Transform function algorithm was applied to the R-R tachogram to obtain the power frequency spectrum. Frequency bandwidths were selected according to recommendations by the Joint Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Malik et al., 1996). Thus, a low-frequency (LF) band was determined as the area between frequencies of 0.04-0.15 Hz while the high frequency (HF) band was taken as 0.15-0.50 Hz under non-exercising conditions. During exercising conditions an extended HF bandwith of 0.15-0.70 Hz was used. The magnitude of either the HF or LF spectral power component was presented either in absolute units (ms^2) or in normalized units (nu) calculated as:

[(Reference component power (ms^2))/(total power (ms^2) - VLF power (ms^2))] *100

where the very low frequency component (VLF) is considered as the area between frequencies of 0.005-0.04 Hz and the total power comprises the area between 0.005 Hz and the upper limit of the HF component (Malik et al., 1996; Malliani et al., 1991). An index of the sympathovagal balance was taken as the ratio of low frequency to high frequency spectral power components (LF/HF).

Treatment of Data and Statistical Analysis

Time and frequency domain variables were obtained for each subject under each of the nine experimental conditions (Figure 1). Subsequently, the group mean and standard error of the mean were calculated for each dependent variable under each separate experimental condition. The time domain variables included the average R-R interval (ms) as well as the standard deviation (SDNN) of successive R-R intervals and R-R interval variance. Similar computations were also derived for beat-to-beat finger systolic and diastolic blood pressures. The frequency domain variables included the HF and LF components of the R-R interval, of the beat-to-beat systolic and diastolic blood pressures expressed either in absolute units (ms^2) or in nu, the LF/HF ratio as well as the peak respiratory frequency (Hz).

The data is expressed as mean ± SEM. Group differences in baseline circulatory parameters (resting heart rate, mean R-R interval, mean R-R variance, diastolic and systolic resting blood pressures) were examined using Student t- tests for unpaired samples. HF and LF power spectral components, the LF/HF ratio as well as peak respiratory frequency responses to controlled respiration, tilt, exercise and exercise recovery were isolated using a series of separate ANOVA. Main effects of group and controlled respiration were determined in both the supine and the seated position using (2X2) ANOVA for repeated measures on the last factor. A similar analysis was also performed to examine the effects of passive head-up tilt. To isolate for the effects of Exercise 100 and 120, a (2X3) ANOVA for repeated measures was performed taking seated values as baseline. Responses to post-exercise Recovery 10 and 20 were examined using Exercise120 as baseline. Upon findings of significant main effects, planned

comparisons were performed using ®Systat statistics package. Group differences in the magnitude of response to each condition were assessed using unpaired t-tests on relative change calculations. Considering the limited sample size due to a restricted number of patients meeting inclusion criteria for the present study and the lack of information concerning heart rate variability in post-operative congenital heart defect patients the statistical significance level was set at $p \leq 0.10$.

RESULTS

Resting descriptive data

Table 1 summarizes the anthropometric and baseline circulatory data in the TOF group and the control group. Age, height, weight, body surface area and body mass index were not significantly different between groups. Moreover, there were no significant differences between either groups for resting heart rate, R-R interval and diastolic and systolic blood pressures.

Circulatory responses

Variations in heart rate (HR), R-R intervals, systolic and diastolic blood pressures (SBP, DBP) throughout all experimental conditions are shown in Table 2. Whether in the supine or seated position, no significant change in these parameters were observed in response to controlled respiration. As expected, results indicate HR to increase in response to passive head-up tilt (HUT) and exercise in both groups. An increase in SBP was found during exercise in both groups as well as in response to passive HUT in TOF patients while a significant fall in SBP was observed in response to HUT in control subjects. In addition, both groups exhibited a decrease in HR, DBP and SBP in recovery from Exercise120. Head-up tilt resulted in a significant increase in DBP in patients but not in control subjects leading to a significant group difference.

Table 2. Circulatory variables throughout all experimental conditions.

		Supine	Sup CR	HUT	Seated	Seat CR	Ex 100	Ex 120	Rec 10	Rec 20
HR (bpm)	TOF	70.6(3.98)	70.8(3.79)	85.5(3.34)**	74.6(3.57)	76.6(3.57)	103.6(0.88)††	122.6(1.43)††##	93.5(4.08)††‡‡	89.0(3.73)††‡‡##
	CTRL	63.7(2.84)	64.6(3.49)	86.3(5.88)**	72.9(4.26)	73.8(4.68)	108.0(2.63)††	123.0(1.16)††##	91.2(4.28)††‡‡	85.8(4.52)††‡‡##
R-R (ms)	TOF	872.1(49.39)	867.6(46.20)	711.2(29.58)**	819.0(40.52)	797.7(39.52)	579.5(4.86)††	489.8(5.67)††##	651.7(28.32)††‡‡	681.5(29.52)††‡‡
	CTRL	955.4(42.03)	947.2(49.41)	717.6(47.54)**	844.3(53.23)	837.7(57.53)	557.5(12.89)††	488.2(4.62)††##	668.9(33.32)††‡‡	714.2(40.97)††‡‡
SBP (mmHg)	TOF	106.2(2.88)	106.6(3.23)	108.7(5.46)	104.4(4.64)	101.6(3.16)	119.6(3.51)††	130.0(2.08)††##	108.9(4.40)‡‡	105.1(4.80)‡‡
	CTRL	109.8(5.17)	111.2(5.28)	101.2(2.20)*	111.5(3.76)	108.8(2.83)	123.8(2.84)††	128.2(1.98)††	115.0(4.16)‡‡	114.8(3.64)‡‡
DBP(mmHg)	TOF	66.9(2.79)	66.0(2.19)	74.1(2.68)**§	70.0(2.56)	69.1(2.47)	74.0(2.98)††	73.8(2.15)†	69.1(2.03)‡‡	68.9(1.90)‡‡§
	CTRL	68.8(2.85)	70.0(2.72)	68.0(1.77)	72.5(2.16)	72.5(2.44)	78.0(2.80)††	77.5(2.32)††	73.5(2.90)‡‡	74.5(2.50)‡

HR= heart rate; R-R= R-R interval; SBP= systolic blood pressure; DBP= diastolic blood pressure; TOF= tetralogy of Fallot subjects; CTRL= control subjects; Sup CR= controlled respiration at 12 breaths/min in the supine quiet rest position; HUT= passive head-up tilt at 85°; Seat CR= controlled respiration at 12 breaths/min in the seated position; Ex 100 and Ex 120= submaximal exercise at a heart rate of 100 and 120 beats/min, respectively; Rec 10 and 20= post-exercise recovery at 10 and 20 minutes, respectively. Mean (SEM)

* $p \leq 0.10$, ** $p < 0.05$ HUT vs. Supine

† $p \leq 0.10$, †† $p \leq 0.05$ Exercise or Recovery vs. Seated

‡ $p < 0.10$, ‡‡ $p < 0.05$ Recovery vs. Ex 120

$p \leq 0.10$, ## $p \leq 0.05$ Successive Exercise or Recovery levels

§ $p \leq 0.10$ TOF vs.CTRL

Time domain parameters

Table 3 shows group means of the average RR variance calculated for all experimental conditions in TOF patients and controls. Examination of individual data indicates systematically lower RR variance in 7 out of 8 TOF patients when compared to their control counterpart under all non-exercising conditions. Under supine baseline conditions, R-R variance was slightly but non-significantly lower in TOF patients compared to control subjects. In the supine position but not in the seated position, controlled respiration resulted in a significantly lower variance in TOF than controls. Variance during passive HUT was found to be lower in patients than controls although it was only marginally significant ($p = 0.11$). A lower variance in TOF patients was also observed during recovery from exercise, yet found to be statistically significant only after 20 minutes of recovery.

Figure 2 illustrates the effects of experimental conditions on peak respiratory frequency (Hz). There were no statistical differences in peak respiratory frequencies between TOF patients and controls for any physiological state. Subjects from both groups adequately followed the imposed breathing rate of 0.20 Hz in both the supine and seated conditions and thus, appear as overlapping circles on Figure 2. Controlled respiration resulted in a significant decrease in peak respiratory frequency in both groups under supine conditions but was found to be significant only in control subjects during seated controlled respiration. As expected, respiratory rate increased significantly during exercise in both groups. Although respiratory rate decreased in recovery from Exercise 120 a significant fall in breathing rate was only seen in controls. In both groups, mean recovery breathing frequencies were found to have returned to pre-exercise seated values.

Table 3. Group means of R-R variance throughout all experimental conditions in tetralogy of Fallot patients and control subjects.

Condition	Variance (ms^2) TOF	Variance (ms^2) CTRL	p Value
Supine	2733.1(885.08)	4585.4(741.09)	0.13
Sup CR	2662.9(765.41)	6803.1(1453.03)	0.03
HUT	1705.4(302.11)	4051.4(1295.53)	0.11
Seated	3382.3(864.29)	5017.7(1360.36)	NS
Seat CR	3344.1(762.68)	6815.6(2751.20)	NS
Ex 100	572.8(105.34)	503.9(100.95)	NS
Ex 120	321.6(86.52)	286.2(88.52)	NS
Rec 10	947.8(202.53)	1724.0(450.51)	0.14
Rec 20	1397.8(252.78)	3485.7(1016.06)	0.08

Values are given as mean (SEM).

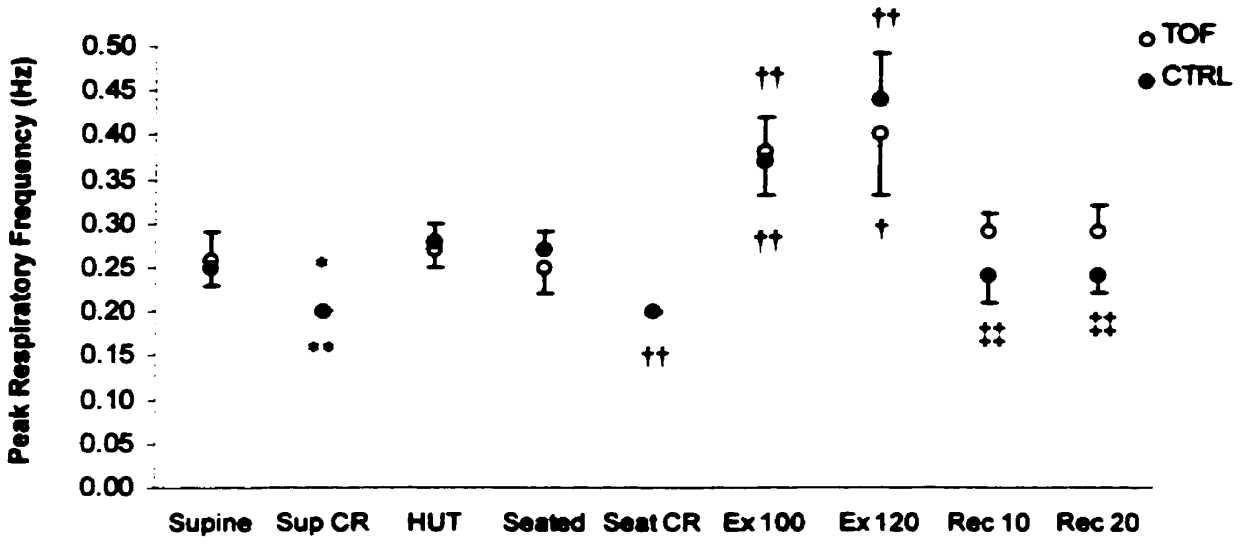


Figure 2. Peak respiratory frequency (Hz) at quiet rest (supine), during controlled respiration at 12 breaths/min or 0.2 Hz (CR), during orthostatic challenges and recovery from exercise in tetralogy of Fallot (TOF, open circles) patients and control (CTRL, closed circles) subjects. HUT = passive 85° head-up tilt; Ex 100 and Ex 120 = submaximal exercise at heart rates of 100 and 120 beats/min; Rec 10 and Rec 20 = post-exercise recovery at 10 and 20 minutes. Data are expressed as means (SEM).

* $p < 0.10$, ** $p < 0.05$ CR vs. Supine

† $p < 0.10$, †† $p < 0.05$ CR or Exercise vs. Seated

‡‡ $p < 0.01$ Recovery vs. Ex 120

Power Spectral Components

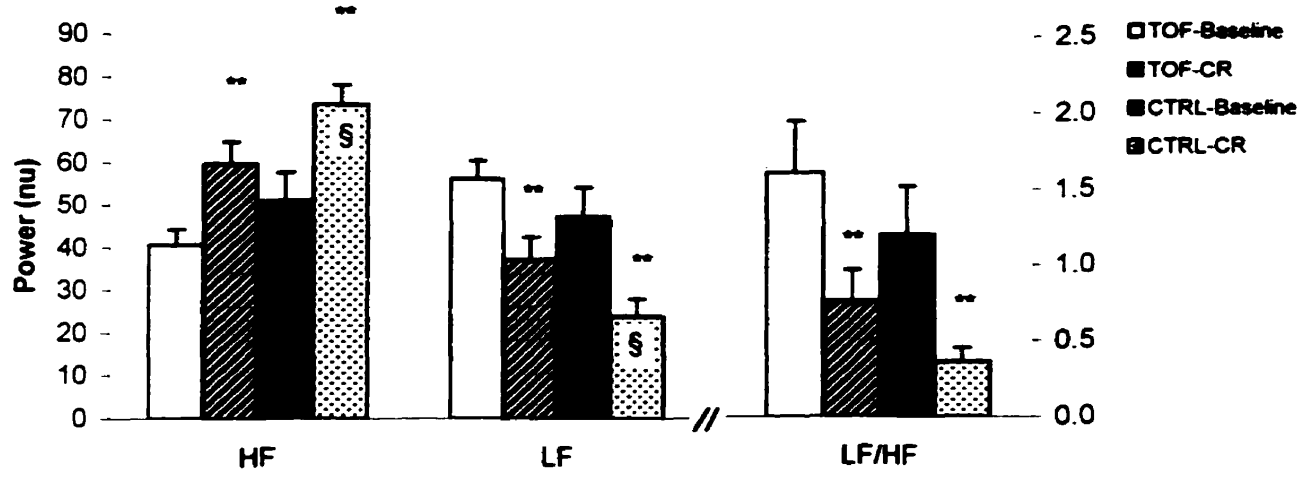
A. *Effect of Controlled Respiration*

Heart Rate Variability

As expected, controlled respiration in the supine position induced a significant increase in the HF and inversely a significant decrease in the LF spectral power components and the LF/HF ratio in both patients and controls (Figure 3A). Results demonstrated a significant increase in the HF component, a decrease in the LF component and LF/HF ratio in both TOF patients and control subjects ($p < 0.05$). Relatives changes in spectral components from baseline were of similar magnitude in both patients and controls; the HF spectral power component increased by 50.0 ± 8.49 and 62.1 ± 24.01% in TOF and controls respectively. Similarly, the LF spectral power component decreased from baseline by 34.0 ± 7.13 and 43.4 ± 10.46% in TOF and controls respectively. Under supine controlled respiration, the HF component (nu) was significantly lower (TOF: 59.6 ± 5.15 vs. CTRL: 73.5 ± 4.55) and conversely the LF component (nu) was significantly higher in TOF patients when compared to controls (TOF: 37.1 ± 5.25 vs. CTRL: 23.7 ± 4.19) ($p < 0.10$). The LF/HF ratio was similarly reduced from baseline in both groups from 1.6 ± 0.34 to 0.8 ± 0.21 in TOF patients (relative change: -52.5% ± 8.86) and from 1.2 ± 0.32 to 0.4 ± 0.09 in controls (relative change: -54.8% ± 12.34). The effects of controlled respiration while seated were similar to those found in the supine position for TOF patients (Figure 3B). However, control subjects showed a significant response in the HF spectral power component only. No significant difference between groups was found for any of the spectral components.

Effect of Controlled Respiration

a) Supine



b) Seated

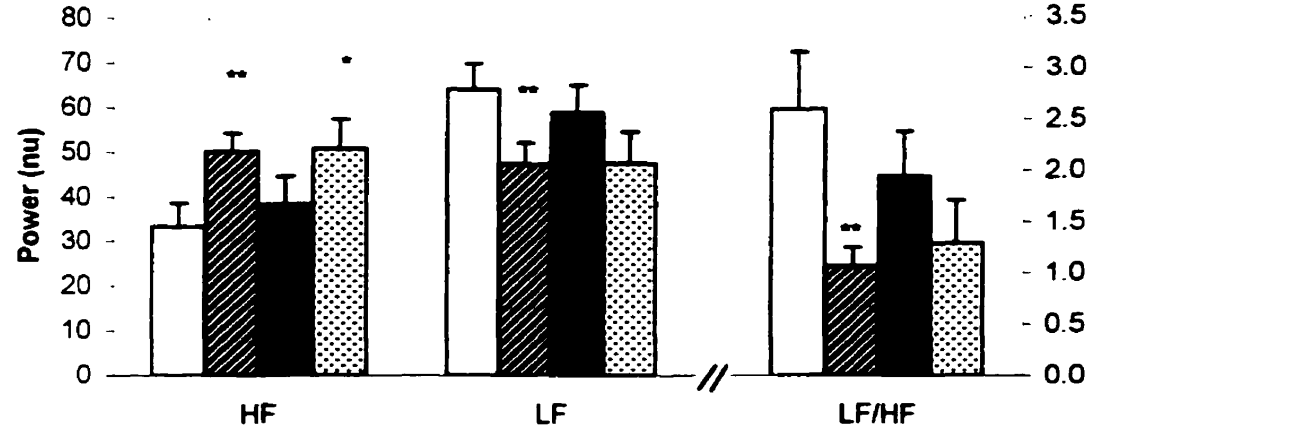


Figure 3. High frequency (HF) power, low frequency (LF) power in nu and the LF/HF ratio of R-R variability during spontaneous and controlled respiration (CR) at 12 breaths/min or 0.2 Hz in the a) supine quiet rest and b) seated conditions in tetralogy of Fallot (TOF) patients and control (CTRL) subjects. nu= normalized units.Data are expressed as means (SEM).
* $p \leq 0.10$, ** $p \leq 0.05$ CR vs. Baseline
§ $p < 0.10$ TOF vs. CTRL

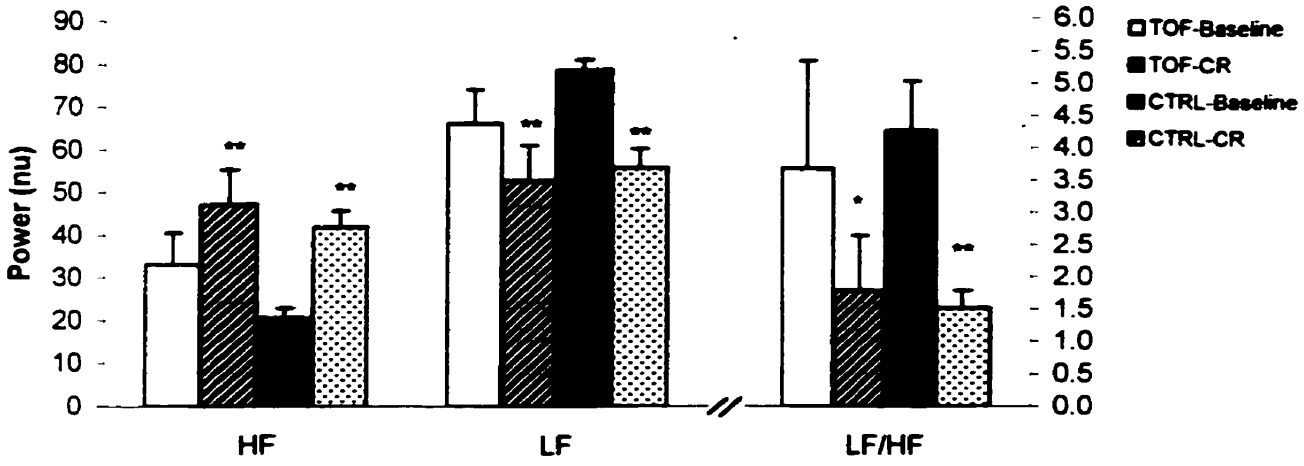
Blood Pressure Variability

Systolic Blood Pressure

Under conditions of supine quiet rest, the total SBP variance was higher in TOF patients 40.5 ± 9.96 $mmHg^2$ than controls 22.7 ± 3.40 $mmHg^2$, although the difference did not reach statistical significance ($p = 0.15$). Figure 4A illustrates the effects of an imposed breathing rate on the HF, LF power spectral components and the LF/HF ratio of SBP variability during supine quiet rest. Results indicated that controlled respiration produced a significant increase in the HF and conversely a decrease in the LF spectral components in both groups ($p < 0.05$). The magnitude of change in the HF component was found to be 2 fold higher in controls than TOF patients (58.0 ± 16.31 vs. 129.5 ± 37.32 %). The LF/HF ratio decreased similarly in both TOF and control subjects. Similar observations were found for controlled respiration in the seated position as shown in Figure 4B. There were no statistically significant group differences for the HF, LF components or LF/HF ratio of SBP variability in either the supine or seated positions.

Effect of Controlled Respiration

a) Supine



b) Seated

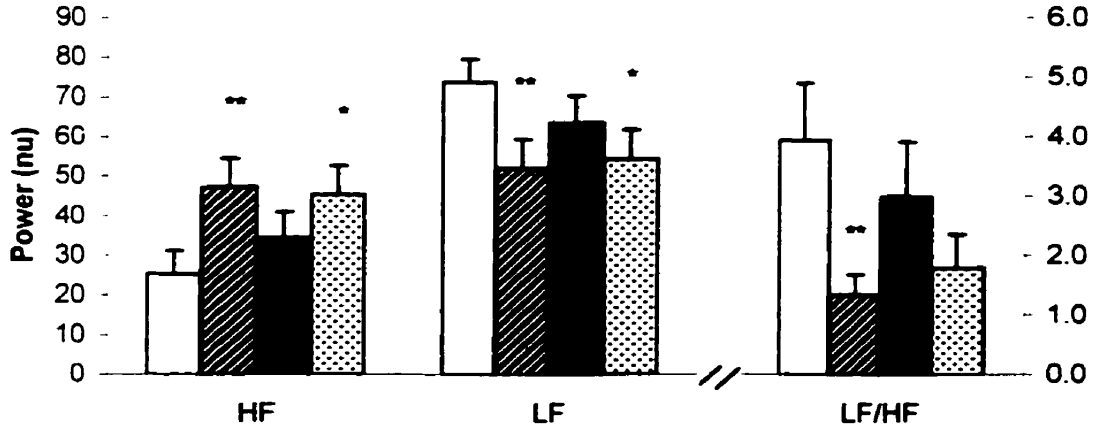


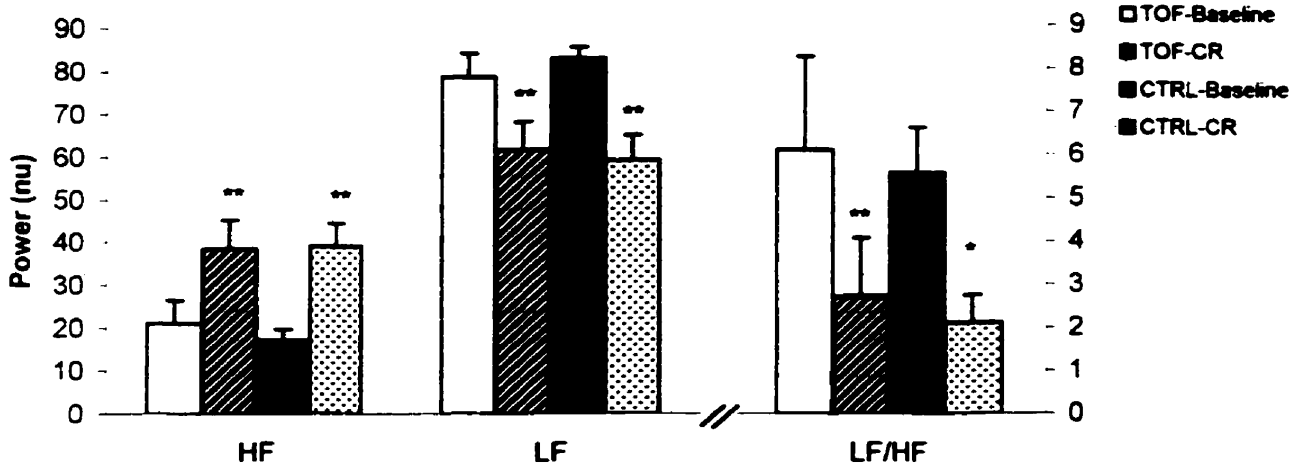
Figure 4. High frequency (HF) power, low frequency (LF) power in nu and the LF/HF ratio of SBP variability during spontaneous and controlled respiration (CR) at 12 breaths/min or 0.2 Hz in the a) supine quiet rest and b) seated conditions in tetralogy of Fallot (TOF) patients and control (CTRL) subjects. nu = normalized units. Data are expressed as means (SEM).
* $p \leq 0.10$, ** $p < 0.05$ CR vs. Baseline

Diastolic Blood Pressure

Under quiet supine baseline conditions, the total DBP variance was not statistically different between groups (TOF: 9.9 ± 2.30; CTRL: 8.1 ± 1.37, $mmHg^2$). Figure 5A and B show the effect of controlled respiration on the HF, LF power spectral components and LF/HF ratio of DBP variability in the supine and seated conditions respectively. Results from Figure 5A indicate an increase of similar magnitudes in the HF component and a decrease in the LF component in both groups ($p < 0.05$). The LF/HF ratio decreased by 51.4 ± 11.94 % and by 54.6 ± 17.91 % in TOF patients and in controls, respectively ($p > 0.05$). Controlled respiration in the seated position resulted in similar DBP spectral component responses as found in the supine position for TOF patients but not for control subjects. A main effect of controlled respiration was not observed in control subjects for either the HF or the LF spectral power components or the LF/HF ratio. Although significant group differences were not observed for any of the spectral components or ratio, a significantly greater relative decrease in the LF component and in the LF/HF ratio ($p \leq 0.10$) from seated baseline were observed in TOF than control subjects in response to the imposed breathing rate.

Effect of Controlled Respiration

a) Supine



b) Seated

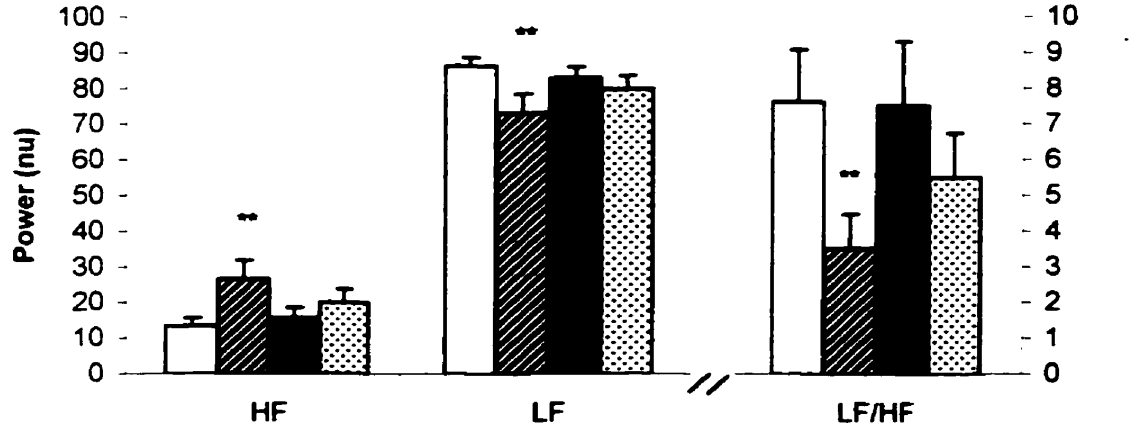


Figure 5. High frequency (HF) power, low frequency (LF) power in nu and the LF/HF ratio of DBP variability during spontaneous and controlled respiration at 12 breaths/min or 0.2 Hz in the a) supine quiet rest and b) seated conditions in tetralogy of Fallot (TOF) patients and control (CTRL) subjects. nu = normalized units. Data are expressed as means (SEM).
* $p < 0.10$, ** $p \leq 0.05$ CR vs. Baseline

B. *Effect of passive Head-up Tilt*

Heart Rate Variability

Figure 6 shows the HF and LF power spectral components and the LF/HF ratio of R-R variability during supine quiet rest and passive 85° HUT. All of the subjects completed the 10 minutes of head-up tilt without any signs of apparent syncope. As expected, there was a significant decrease in the HF component and conversely a significant increase in the LF component of R-R variability as well as a significant increase in the LF/HF ratio in both TOF patients and control subjects. Both groups exhibited similar changes in magnitude on the HF (TOF: - 49.0 ± 11.12 vs. CTRL: -47.5 ± 16.85, %), LF (TOF: +48.4 ± 12.53 vs. CTRL: +79.4 ± 25.00, %) power spectral components and LF/HF ratio (TOF: +345 ± 122.9 vs. CTRL: +410 ± 91.4, %) in response to tilting. There was no statistical difference between groups for any of the spectral components.

Blood Pressure Variability

Systolic Blood Pressure

Head-up tilt induced no significant main effect on either the HF, LF or the LF/HF ratio of the SBP spectral components in either control subjects or TOF patients. Similarly, no significant main group difference was observed for any of the spectral indices of SBP variability.

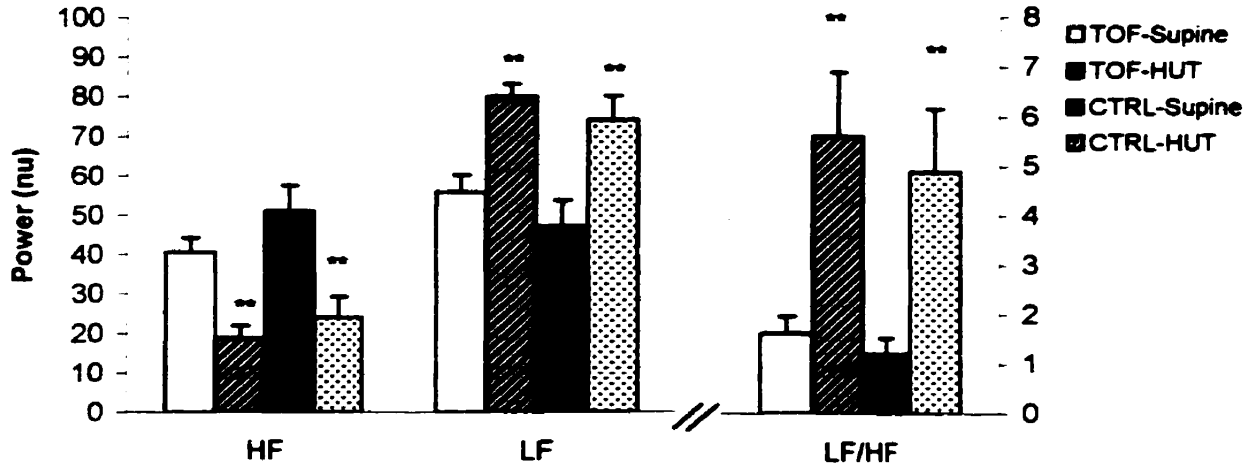


Figure 6. High frequency (HF) power, low frequency (LF) power in nu and the LF/HF ratio of R-R variability at quiet rest (supine) and during passive 85° head-up tilt (HUT) in tetralogy of Fallot (TOF) patients and control (CTRL) subjects. nu = normalized units. Data are expressed as means (SEM).
** $p < 0.05$ HUT vs. Supine

Diastolic Blood Pressure

Figure 7 shows the HF, LF power spectral components and LF/HF ratio of DBP variability from supine quiet rest to passive 85° HUT. At 85° HUT, the total DBP variance was significantly ($p < 0.05$) higher in TOF patients than control subjects (28.6 ± 5.00 vs. 12.8 ± 2.18, $mmHg^2$) respectively. Results indicate a significant decrease in the HF component and increases in the LF component and LF/HF ratio in TOF patients only. No significant condition effect was observed in control subjects. Similarly, no main effect for group was observed.

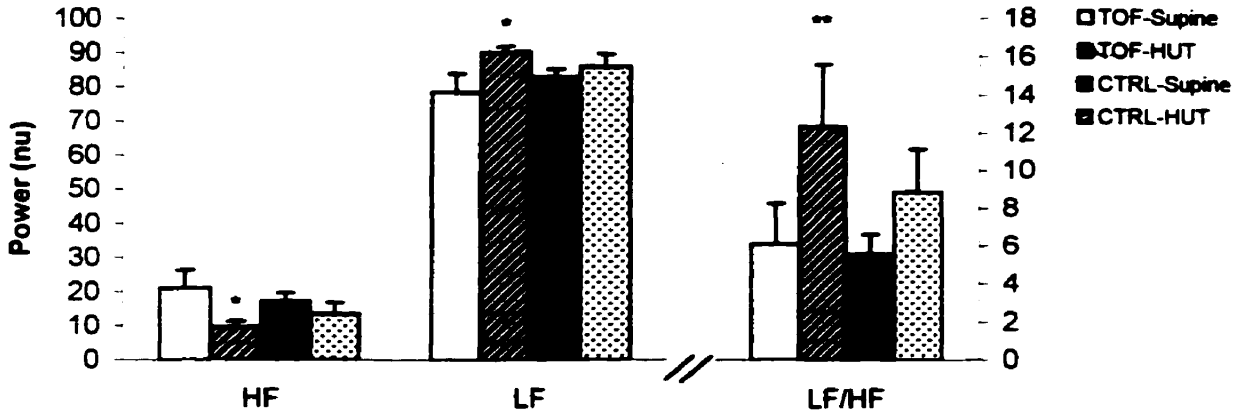


Figure 7. High frequency (HF) power, low frequency (LF) power in nu and the LF/HF ratio of DBP variability at quiet rest (supine) and during passive 85° head-up tilt (HUT) in tetralogy of Fallot (TOF) patients and control (CTRL) subjects. nu = normalized units. Data are expressed as means (SEM). * $p < 0.10$, ** $p < 0.05$ HUT vs. Supine

C. *Effect of Dynamic Exercise*

Heart Rate Variability

As expected, mean R-R interval duration and variance decreased ($p < 0.05$) in both groups in response to cycling exercise compared to the seated resting position. Control subjects achieved slightly higher exercise loads than TOF patients (100 bpm: 53.2 ± 8.30 vs. 37.0 ± 3.95; 120 bpm: 76.4 ± 10.41 vs. 62.5 ± 5.54, Watts) respectively, the difference between groups being only marginally significant ($p \leq 0.10$) for the lower exercise level.

Figure 8 compares the HF and LF spectral power components under seated baseline condition, low and medium intensity exercise and recovery. As expected, exercise resulted in a significant decrease in the HF component and conversely an increase in the LF component in both groups ($p < 0.05$). From seated baseline to Exercise 100, the HF component was similarly reduced (TOF: 31.8 ± 12.31 vs. CTRL: 32.4 ± 12.65, %) and the LF component similarly increased (TOF: 31.7 ± 13.26 vs. CTRL: 40.1 ± 14.25, %) in both groups resulting in a similar increase in the LF/HF ratio. There was no significant group difference. At Exercise 120, TOF patients demonstrated a further significant decrease in the HF component and increase in the LF spectral power component and LF/HF ratio (Figure 9) while control subjects only showed a slight change in spectral power components from the previous exercise load. A significant group effect was observed at the Exercise 120 level for both spectral components and LF/HF ratio.

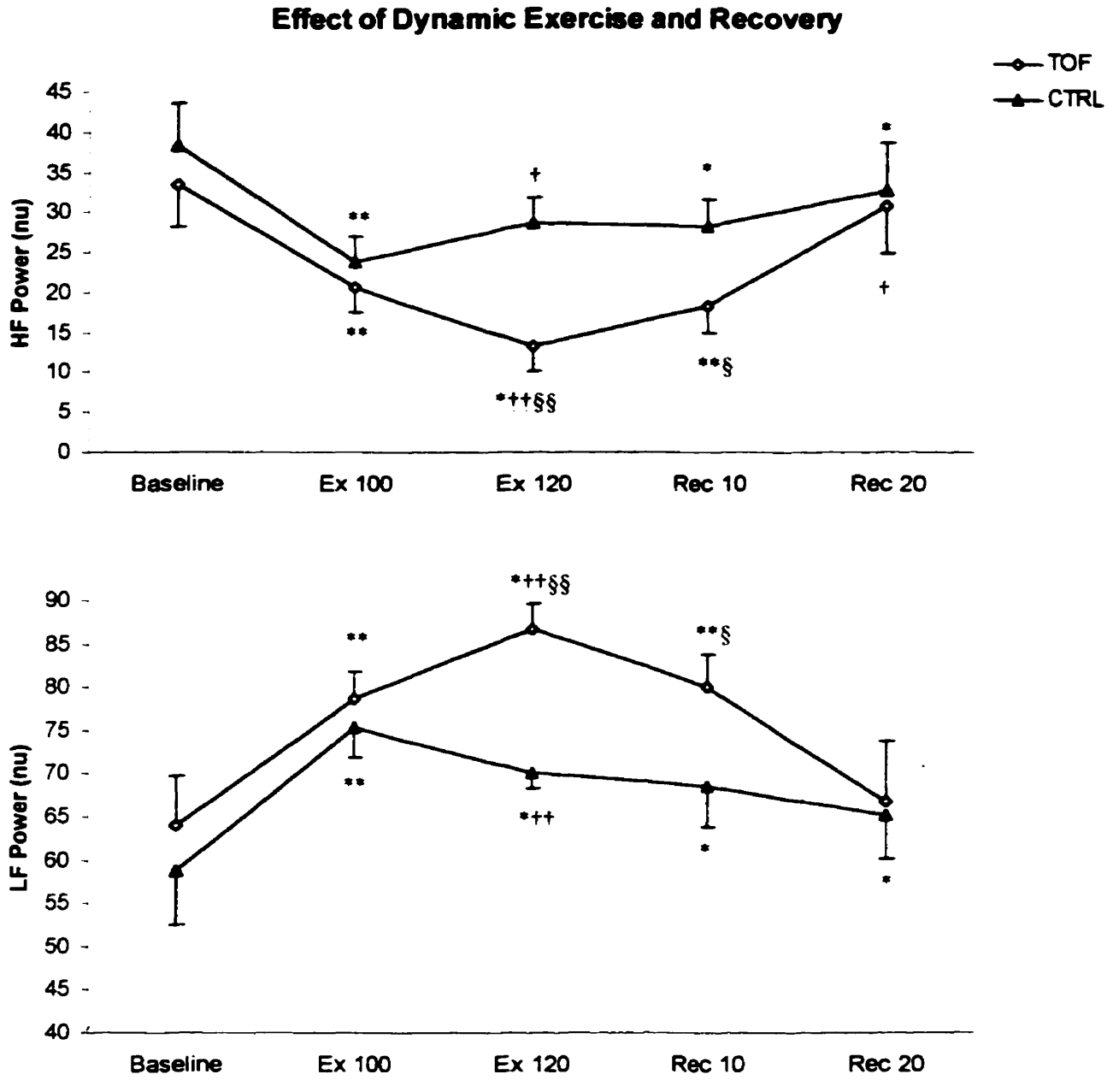


Figure 8. High frequency (HF) power and low frequency (LF) power in nu of R-R variability at baseline (seated), during exercise and following cessation of exercise in tetralogy of Fallot (TOF, open lozanges) patients and control (CTRL, closed triangles) subjects. nu = normalized units. Ex 100 and Ex 120 = submaximal exercise at heart rates of 100 and 120 beats/min; Rec 10 and Rec 20 = post-exercise recovery at 10 and 20 minutes. Data are expressed as means (SEM).

* $p \leq 0.10$, ** $p < 0.05$ Exercise or Recovery vs. Baseline

† $p \leq 0.10$, †† $p \leq 0.05$ Successive Exercise or Recovery conditions

§ $p \leq 0.10$, §§ $p < 0.05$ TOF vs. CTRL

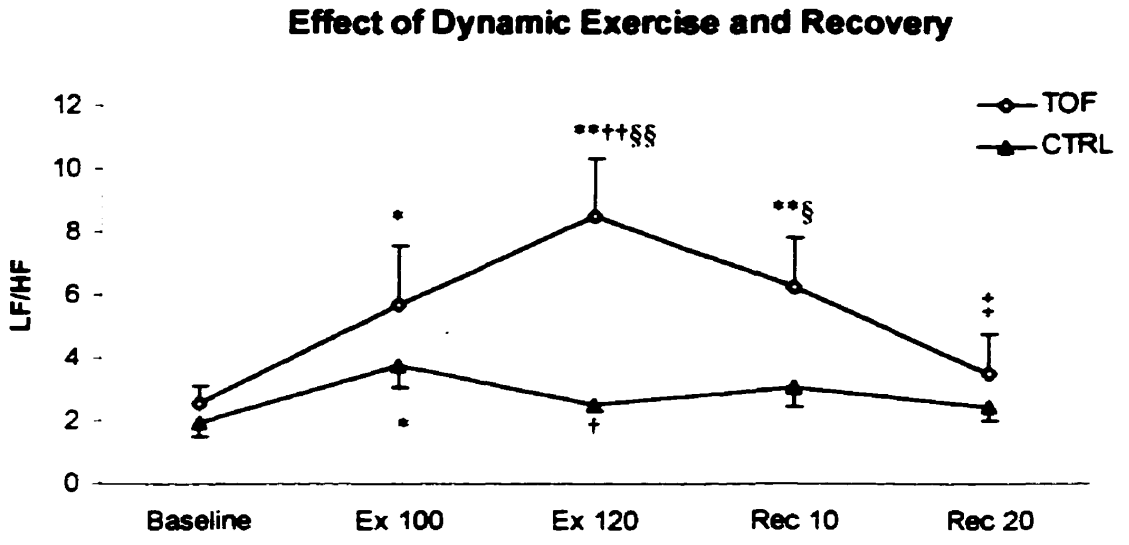


Figure 9. The LF/HF ratio of R-R variability at baseline (seated), during exercise and following cessation of exercise in tetralogy of Fallot (TOF, open lozanges) patients and control (CTRL, closed triangles) subjects. NU= normalized units. Ex 100 and Ex 120 = submaximal exercise at heart rates of 100 and 120 beats/min; Rec 10 and Rec 20 = post-exercise recovery at 10 and 20 minutes. Data are expressed as means (SEM).
* $p < 0.10$, ** $p < 0.05$ Exercise or Recovery vs. Baseline
† $p \leq 0.10$, †† $p \leq 0.05$ Successive Exercise or Recovery conditions
‡ $p < 0.10$ Rec 20 vs. Ex 120
§ $p \leq 0.10$, §§ $p < 0.05$ TOF vs. CTRL

Figure 10 illustrates the relative percentage changes in the HF and LF spectral power components as a results of steady-state exercise from the seated position. Results indicate similar magnitude of change from baseline in the LF power component between TOF patients and control subjects at both exercise levels. Relative changes from baseline in the HF component were also similar between groups, however a further relative decrease was observed in TOF patients at the Exercise 120 level. This resulted in significantly opposed responses between successive exercise levels of 100 and 120 bpm in both the HF and LF spectral components for TOF patients and control subjects. Similar observations were also found for the LF/HF ratio (Figure 11).

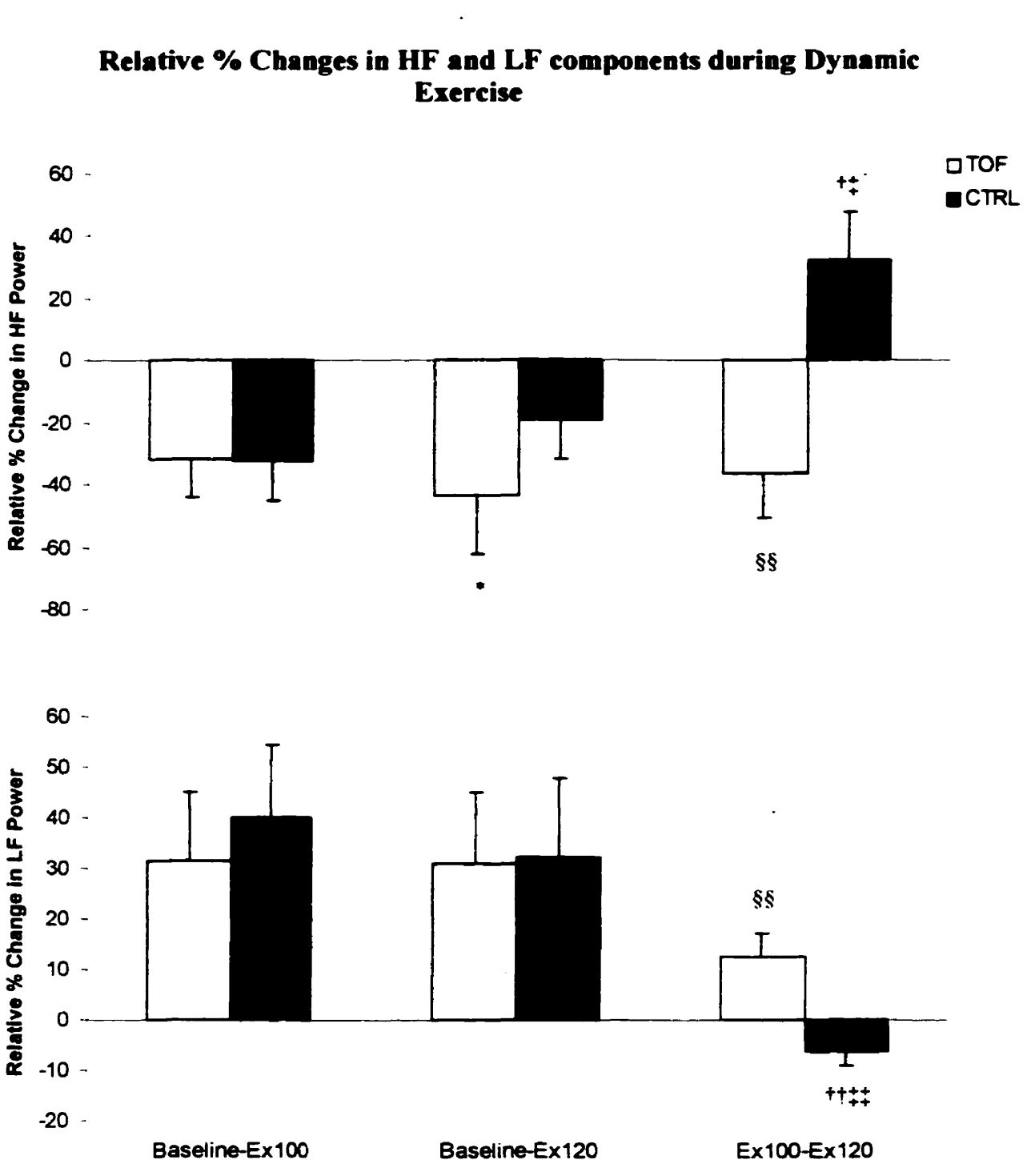


Figure 10. Relative percent change in HF power and LF power of R-R variability on the effects of steady-state exercise from baseline (seated) and within both levels of exercise in tetralogy of Fallot (TOF, open bars) patients and control (CTRL, closed bars) subjects. Ex 100 and Ex 120 = submaximal exercise at heart rates of 100 and 120 beats/min. Data are expressed as means (SEM).

* $p < 0.10$ Baseline-Ex120 vs. Baseline-Ex100

† $p < 0.10$, †† $p < 0.05$ Ex100-Ex120 vs. Baseline-Ex100

‡ $p < 0.10$, ‡‡ $p < 0.05$ Ex100-Ex120 vs. Baseline-Ex120

§§ $p < 0.05$ TOF vs. CTRL

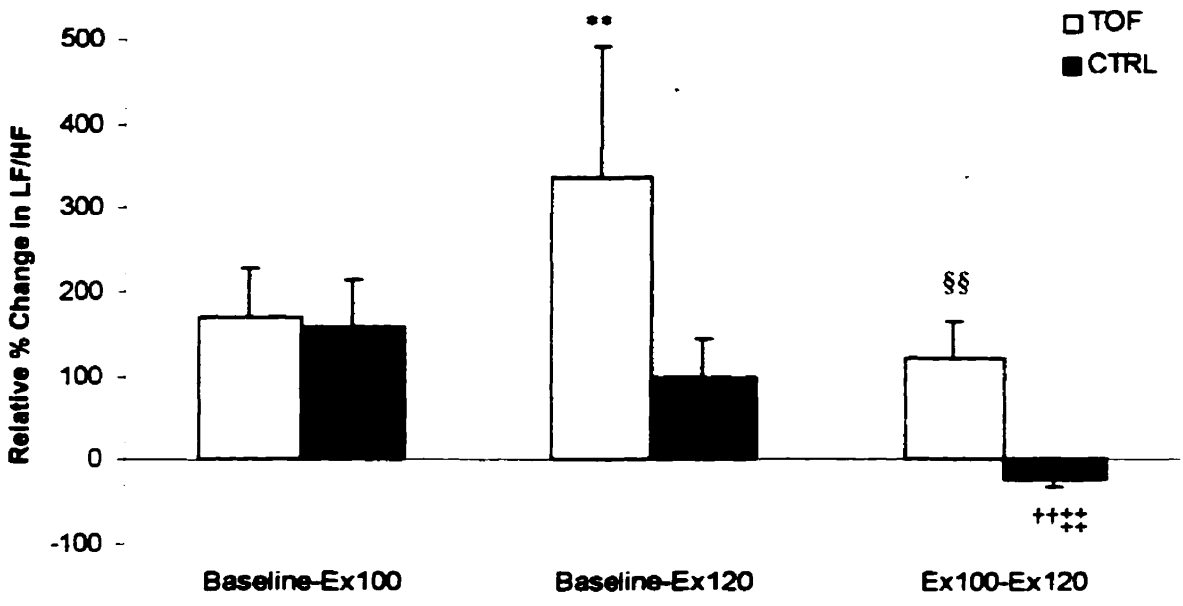


Figure 11. Relative percent change in the LF/HF ratio of R-R variability on the effects of steady-state exercise from baseline (seated) and within both levels of exercise in tetralogy of Fallot (TOF, open bars) patients and control (CTRL, closed bars) subjects. Ex 100 and Ex 120 = submaximal exercise at heart rates of 100 and 120 beats/min. Data are expressed as means (SEM).

** $p < 0.05$ Baseline-Ex120 vs. Baseline-Ex100

†† $p < 0.05$ Ex100-Ex120 vs. Baseline-Ex100

‡‡ $p < 0.05$ Ex100-Ex120 vs. Baseline-Ex120

§§ $p < 0.05$ TOF vs. CTRL

D. *Effect of Passive Post-Exercise Recovery*

Heart Rate Variability

As expected, HF and LF power spectral components returned towards pre-exercise levels during passive recovery. Figure 8 illustrates the effect of recovery on the HF and LF components of R-R variability in TOF patients and control subjects. Comparisons of HF and LF spectral power components obtained after 10 minutes and 20 minutes of recovery to those computed for the highest exercise load indicated that both spectral components of TOF patients returned to baseline values by 20 minutes of recovery. In control subjects slight differences from seated baseline ($p < 0.10$) were observed after both 10 and 20 minutes of recovery for both spectral components. A significant group difference was found after 10 minutes post-exercise; control subjects showing a higher HF component (28.2 ± 4.11 vs. 18.2 ± 3.29, nu) and a lower LF component (68.5 ± 4.76 vs. 80.0 ± 3.67, nu) than TOF patients. Subsequently, the LF/HF ratio was higher in TOF patients than control subjects (6.2 ± 1.60 vs. 3.1 ± 0.66) (Figure 9).

DISCUSSION

Results from this study showed TOF patients to have an overall lower total R-R variance than control subjects under all non-exercising conditions. Spectral frequency decomposition indicate the HF vagally mediated component to be slightly lower in patients under spontaneous breathing conditions; values becoming statistically significant under conditions of controlled respiration. Head-up tilt decreased total R-R variance more in TOF patients than control subjects although both groups exhibited similar sympathovagal balance. Total R-R variance during steady-state exercise was similar in both groups yet spectral decomposition indicated a significantly higher LF component during moderate exercise in TOF patients.

Heart rate variability: baseline status, responses to controlled respiration, head-up tilt, and exercise.

To our knowledge there exists very few publications regarding heart rate variability in patients with a congenital heart defect, prior to or following surgical repair. In one of only two reports published to date, Finley et al. (1989) examined heart rate variability during 10-15 minute recordings in both the supine and standing positions in young patients prior to and 5 months following surgical repair of atrial septal defect. Results showed patients to have lower total variability and HF spectral power compared to their age-matched healthy counterparts, yet post-operative heart rate variability was increased compared to pre-operative findings. In the other study, Gordon et al. (1988) obtained continuous recordings over a mean period of 9 hours immediately following corrective surgery for a variety of congenital heart diseases. Patients were divided into

those with uncomplicated postoperative clinical courses and those who had sustained cardiac arrest. Results indicated patients from the latter group to have spectral patterns significantly different from the other patient group.

Results from the present study of post-operative TOF patients tend to confirm observations of Finley et al. (1989). Overall, R-R variance was found to be lower in 7 of 8 patients when compared to their age-matched control counterparts for all non-exercising conditions and average baseline HF values of heart rate variability were statistically lower in patients when breathing rate was standardized to minimize power dispersion. With resting heart rate variability resulting primarily from vagally mediated respiratory sinus arrhythmia, the present results may be taken to suggest a lower sinoatrial vagal influence in TOF patients.

A reduced heart rate variability and HF spectral power have been commonly reported in many clinical settings (Casolo et al., 1991; Huikuri et al., 1993; Kienzle et al., 1992) and has been associated with an increased risk of arrhythmic event (Algra et al., 1993; Bigger et al., 1992; Farrell et al., 1991; Huikuri et al., 1993). Cardiac autonomic status is known to influence the frequency of atrial and ventricular ectopic beats leading to supraventricular tachyarrhythmias. A greater incidence of arrythmic events is indeed reported in post-operative TOF (Perry & Garson, 1995) patients which is in agreement with the predictive outcome of a lower baseline HRV. In the present study however, patients were carefully selected to include only those exhibiting an excellent post-operative clinical status free of resting arrhythmic events.

On the other hand, patients operated for TOF commonly typically exhibit a right bunble branch block conduction abnormality (Perry & Garson, 1995; Walsh et al., 1988)

leading to widening of the QRS complex. Whether this affects R-R variability remains unknown. While the wider QRS associated with the right bundle branch block lengthens the overall electrocardiographic conduction cycle, it would appear unlikely to affect the R-R interval fluctuations.

Response to HUT:

As expected, tilting reduced the overall HRV in both groups but to a greater extent in patients. In as much as vagally mediated respiratory sinus arrhythmia is the main component of resting HRV, the greater observed tilt-induced reduction in HRV may be the result of lower baseline parasympathetic influences. Decomposition of the heart rate variability spectrum indicate a predominant sympathovagal balance during HUT which appears similar in both groups although results show a slightly but non-significantly higher LF component in patients. The present responses to tilting are compatible with previous reports (Furlan et al., 1993; Montano et al., 1994; Pitzalis et al., 1996) showing sympathetic excitation and vagal withdrawal and may be thus taken to reflect the sympathetic influences on the LF component of HRV which at rest are usually only detectable in standing. Low frequency blood pressure oscillations occurring at a rate of 6 to 9 cycles/min have been described in animals by Mayer (1876) which in turn may account for the low frequency influences on heart rate variability (Akselrod et al., 1985). Results from the present study indicate a significant effect of HUT on DBP variability resulting in a significant increase in the LF component in patients but not in control subjects. Diastolic blood pressure variability is dependent on SBP variability and R-R interval variability as well as on total peripheral resistance with the time constant with which DBP is attained. When heart rate

variability was abolished using atrial pacing in dogs, HF variations in arterial blood pressure was diminished by two orders of magnitude while low frequency fluctuations were not found to be dependent of changes in HRV but rather to reflect variability in peripheral vasomotor activity (Akselrod et al., 1985). The increase in the LF power in the upright position may thus be attributed to either an increased amplitude of LF fluctuations in blood pressure or to an increased gain of the baroreceptor in the upright posture (Pagani et al., 1986). A limited increase in heart rate seen in patients might result in variances in R-R interval variability and SBP variability in turn affecting DBP variability. Indeed, while tilting resulted in a 35% increase in heart rate in control subjects, only a 20% increase in heart rate was seen in patients in response to similar variations in pulse pressure. Acute and chronic beta adrenergic blockage with propranolol have been shown to blunt the marked increase in LF power that normally occurs during head-up tilt suggesting that the increase in LF power in the upright position is due to increase cardiac sympathetic nerve activity (Pagani et al., 1986). Thus, an impairment in cardiac sympathetic efferent influences could account for the observed chronotropic limitation during head-up tilt which may also be related to the abnormal heart rate responses reported in post-operative TOF patients in response to lower-body negative pressure application (Johnson et al., 1997) or to maximal exercise (Cumming, 1993; Perrault & Drblik, 1989).

Response to Exercise:

In agreement with previous reports, exercise resulted in a significant decrease in total HRV expressed in absolute units (ms^2) (Bernardi et al., 1990; Casadei et al., 1995; Casadei et al., 1996; Lucini et al., 1995). However, while a lower total HRV was typically

found in TOF under most experimental conditions, a similar total HRV was seen in patients and control subjects during exercise, suggesting a similar degree of vagally mediated respiratory influences. Thus, while there was less parasympathetic influences in non-exercising conditions, it appears that the exercise-induced increase in heart rate reduced heart rate variability to the same level in both groups. In response to the first exercise load, a significant decrease in the HF and conversely an increase in the LF R-R spectral components were observed in both TOF patients and control subjects. The fall in the HF component during mild exercise both in absolute and normalized units is in agreement with most authors (Bernardi et al., 1990; Casadei et al., 1995; Lucini et al., 1995) while the increase in the LF component is also found by most except for Hartikainen et al. (1997), who reported a decrease. As found by others (Arai et al., 1989; Radaelli et al., 1996; Yamamoto et al., 1991) an increase from the sitting baseline pattern was also found in the LF/HF ratio.

As reported by many authors, normalized units of LF, HF components or the LF/HF parameters remain unchanged upon increasing exercise intensity in control subjects. In patients however a significant further fall in the HF and conversely an increase in the LF component was observed. The persistence or an increase in the HF component with the use of normalized units during moderate exercise has been reported (Bernardi et al., 1990; Casadei et al., 1995) and has been related to non-neural factors in respiratory sinus arrhythmia associated with ventilation (Bernardi et al., 1990; Casadei et al., 1995; Casadei et al., 1996). In the present study exercising breathing rates were not different between groups and thus cannot account for a lower HF spectral component in TOF patients.

As for HUT, the greater LF component of TOF may thus be related to an increased amplitude of LF fluctuations in blood pressure during exercise. Alternately, the higher LF R-R component may be related to the need for a greater degree of sympathetic influence in patients to achieve the same exercise heart rate as a result of a lower β-adrenergic responsiveness in patients operated for TOF. A decrease in myocardial β_1-density has been reported in congenital heart disease patients with cyanotic as well as acyanotic heart diseases prior to surgical correction (Kozlik et al., 1991a; Kozlik et al., 1991b; Kozlik-Feldman et al., 1993). This was found to be associated with elevated plasma noradrenaline levels which results from a cardiac presynaptic overspill in an attempt to maintain cardiac output. Whether this abnormality is completely reversed after surgical repair has to our knowledge not been verified. Similarly, positioning of atrial cannulae for extra-corporeal circulation during surgical correction has been found to be associated with impairments in the sinoatrial histological integrity; the post-operative reversibility of which has not been verified. While vagal withdrawal may be sufficient to achieve an exercise heart rate of 100 beats/minute accounting for the similarity of response between groups at the first exercise level additional sympathetic stimulation might be necessary to further increase exercising heart rate.

Limitations.

In light of the strict exclusion criteria, the present recordings have been obtained on a small number of patients only. The significance of the present observations in terms of predictive outcome for arrhythmic events remains to be verified in a larger group of post-operative TOF patients exhibiting varying degrees of post-operative clinical status.

Heart rate and blood pressure variability provide a means for the non-invasive indirect assessment of sympathovagal balance. The use of a pharmacological approach using parasympathetic blockage or adrenergic responsiveness to isoproterenol administration may be used to further substantiate the present observations.

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