Improvements in heart rate variability with exercise therapy

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Heart rate variability (HRV) is a noninvasive, practical and reproducible measure of autonomic nervous system function. A heart rate that is variable and responsive to demands is believed to bestow a survival advantage, whereas reduced HRV may be associated with poorer cardiovascular health and outcomes. In recent years, many researchers have investigated the prognostic implications of HRV in a variety of clinical populations. Evidence suggests that reduced HRV has prognostic significance for individuals with myocardial infarction, chronic heart failure, unstable angina and diabetes mellitus. Interventions to increase HRV, such as exercise therapy, have also been examined. The findings of the present review suggest that exercise therapy may improve HRV in myocardial infarction, chronic heart failure and revascularization patients by increasing vagal tone and decreasing sympathetic activity. One hypothesis is that a shift toward greater vagal modulation may positively affect the prognosis of these individuals. While the underlying mechanisms by which exercise training improves vagal modulation are speculative at present, angiotensin II and nitric oxide may be potential mediators.

Key Words: *Autonomic nervous system; Exercise therapy; Heart rate variability; Prognostic*

Les améliorations de la variabilité de la fréquence cardiaque grâce à la rééducation par l'exercice

La variabilité de la fréquence cardiaque (VFR) est une mesure non effractive, pratique et reproductible de la fonction du système nerveux autonome. On pense qu'une fréquence cardiaque variable et réactive aux exigences confère un avantage pour la survie, tandis qu'une VFC réduite pourrait s'associer à une moins bonne santé cardiovasculaire et à des issues plus négatives. Ces dernières années, de nombreux chercheurs ont exploré les conséquences pronostiques de la VFC dans diverses populations cliniques. Selon les données probantes, une VFC réduite a une signification pronostique pour les personnes ayant un infarctus du myocarde, une insuffisance cardiaque chronique, une angine instable et un diabète. Les interventions visant à accroître la VFC, telles que la rééducation par l'exercice, ont également fait l'objet d'un examen. D'après les observations de la présente analyse, la rééducation par l'exercice peut améliorer la VFC en cas d'infarctus du myocarde, d'insuffisance cardiaque chronique et de revascularisation, car elle accroît le tonus vagal et réduit l'activité sympathique. On postule qu'une transition vers une modulation vagale accrue pourrait avoir un effet positif sur le pronostic de ces personnes. Les mécanismes sous-jacents par lesquels l'entraînement à l'exercice améliore la modulation vagale demeurent encore spéculatifs, mais l'angiotensine II et le monoxyde d'azote pourraient constituer des médiateurs potentiels.

In 1965, Hon and Lee (1) were the first to describe the significance of heart rate variability (HRV) in the clinical setting. They noted that reduced beat-to-beat variation of the fetal heart was associated with fetal distress before a detectable change in heart rate. Over the years, reduced HRV has been found to be associated with the development of many cardiovascular conditions, including coronary artery disease (2), hypertension (3), chronic heart failure (CHF) (4) and myocardial infarction (MI) (5), as well as poorer cardiovascular outcomes in those who already have disease (6-9). In contrast, a heart rate that is variable and responsive to demands is believed to bestow a survival advantage (10). Since the 1990s, there has been plenty of research on the prognostic implications of HRV in clinical populations. Interventions to increase HRV, such as exercise therapy, have also been examined given the theoretical plausibility that improvements in HRV may lead to improved outcomes. The purpose of the present review is to describe the principles underlying HRV, describe the parameters used to assess HRV, discuss the prognostic value of HRV in clinical populations, discuss the use of exercise therapy as a method of HRV modification in clinical populations, and discuss the potential mechanisms by which exercise therapy may modify the HRV of individuals with a variety of clinical conditions.

PRINCIPLES UNDERLYING HRV

HRV is a noninvasive, practical and reproducible measure of autonomic nervous system function (11). Although heart rate may be reasonably stable, the time between two heart beats can be considerably different. HRV is the beat-to-beat variation in time of consecutive heartbeats expressed in normal sinus rhythm on electrocardiogram recordings, ranging from a few minutes to 24 h (10-12).

HRV is believed to correspond to the balance between the sympathetic and parasympathetic influences on the sinoatrial node's intrinsic rhythm (12). The ability of the autonomic nervous system and sinoatrial node to respond dynamically to environmental changes results in increased HRV and generally indicates a healthy heart. A reduction in HRV is believed to indicate an inability or attenuation in the autonomic nervous system's or sinoatrial node's responsiveness to change (11).

HRV ASSESSMENT

Time domain measures are the original and simplest method for deriving HRV (12). Time domain measures plot HRV as the change in normal R wave to R wave (N-N) intervals over time (13). Power spectral analysis or frequency domain analysis is another commonly used method for assessing HRV. This method involves plotting the frequency at which the length of the N-N interval changes (13). Cyclic fluctuations of the N-N intervals are computed by the fast Fourier transformation or autoregression (complex demodulation) (14). Novel spectral and nonlinear HRV measures are more recent approaches for measurement of HRV. Novel spectral indexes of HRV include V_{index} and prevalent low-frequency oscillation of heart rate. Nonlinear HRV indexes include alpha-1 (α_1), beta (β) and the ratio of intermediate-term variability to short-term variability (SD12). They represent the structure of heart rate time series as opposed to the amount of HRV at a particular period of time, as is measured with the time and frequency domain parameters (8,15). Each of these HRV assessment techniques is described in Table 1. For a more in-depth methods description of HRV measures, the reader is referred to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (5); Lahiri et al (16); Seely and Macklem (17); and Stein and Reddy (18).

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TABLE 1
Selected heart rate variability (HRV) measures

Parameter	Unit	Description	Frequency
Time domain measures			
SDNN	ms	SD of all normal R wave to R wave (N-N) intervals	
SDANN	ms	SD of 5 min average N-N intervals	
SDNN index	ms	Mean of the SDs for 5 min segments	
rMSSD	ms	Square root of the mean of the sum of squares of successive N-N interval differences. Reflects vagal modulation	
NN50	ms	Number of pairs of adjacent N-N intervals differing by >50 ms. Reflects vagal modulation but is less commonly used in recent studies	
pNN50	%	Number of successive N-N intervals differing by >50 ms divided by the total number of successive N-N intervals. Reflects vagal function	
Frequency domain measures			
HF	ms^2	Power in the high-frequency range. Reflects vagal function. Calculated for recordings ≥5 min	0.15–0.40 Hz
LF	ms^2	Power in the low-frequency range. May reflect a combination of sympathetic and parasympathetic input. Calculated for recordings ≥5 min	0.04–0.15 Hz
VLF	ms^2	Power in the very low-frequency range. Calculated for recordings ≥5 min	0.0033–0.04 Hz
ULF	ms^2	Power in the ultra low-frequency range. Calculated for recordings ≥24 h	<0.0033 Hz
TP	ms^2	Variance of all N-N intervals. Calculated for recordings ≥24 h	~≤0.4 Hz
LF/HF ratio		Ratio of low-frequency to high-frequency. May reflect sympathovagal balance. Smaller ratios may represent parasympathetic dominance and larger ratios may represent sympathetic dominance	N/A
Spectral indexes			
V_{index}	ms^2	An average HF power derived from the most linear segment of HF power against the R-R interval regression curve. It is an HF spectral measure of vagal activity	
PLF	Hz	Analyzed from power spectra of all 5 min periods and represents the frequencies of all maximum peaks within the LF band detected at a resolution of 1/60 Hz averaged over an entire 24 h recording. A shift toward higher LF band frequencies is observed in high-risk patients (26)	
Nonlinear indexes			
α_1		Uses the detrended fluctuation analysis technique of HRV for short- and intermediate-term scaling properties. It detects the presence or absence of fractal-like scaling properties. It is a quantitative method for assessing the extent to which a time series is random at the one end and correlated at the other. Values range from 0.5 (random) to 1.5 (correlated). Values just over 1 are considered normal (8,15)	
β		Assesses the power-law relationship of HRV for long-term fluctuations. Power-law analysis plots the log of spectral power against the log of frequency using spectral analysis data (15,17)	
SD12		Quantifies the shape of the Poincaré plot. The Poincaré plot corresponds graphically to the underlying pattern of the R-R interval time series. This nonlinear index plots the amount of time between two adjacent heart beats versus the amount of time between the subsequent two adjacent heart beats. SD12 is the ratio of the lengths of the axes of an imaginary ellipse. The hub of the ellipse is the average R-R interval of the time series. This ratio is fitted to the Poincaré plot. SD12 is the ratio of intermediate-term variability to short-term variability. It is considered to be an intermediate-term nonlinear measure (8,18)	

α_1 Alpha-1; β Beta; N/A Not applicable

PROGNOSTIC VALUE OF HRV IN CLINICAL POPULATIONS

MI

Researchers have extensively used time domain parameters to assess the prognostic significance of HRV in individuals with an MI (Table 2). In a retrospective analysis of 1284 MI patients, La Rovere et al (19) found that a 24 h SD of all N-N intervals (SDNN) of less than 70 ms significantly and independently predicted cardiac mortality (RR 3.2; 95% CI 1.6 to 6.3). Reduced SDNN and reduced square root of the mean of the sum of squares of successive N-N interval differences have also been reported as independent predictors of mortality in several additional studies (9,20-22). Short-term (5 min) HRV studies have also been performed in this population, with similar findings (23). It is worth noting that 24 h SDNN was not found to be predictive of mortality in high-risk patients with a recent MI, regardless of whether the individual received an implantable cardioverter defibrillator (24). Discrepant findings in this study may be attributable to the inclusion of such high-risk subjects.

Decreased ultra low-frequency power (ULF), very low-frequency power, low-frequency power (LF) and/or variance of all N-N intervals have been found to be independently predictive of mortality in patients who experienced an MI (8,9,15,25-27). Tapanainen et al (15) reported that ULF (less than 8.45 ln ms^2), very low-frequency power (less than 5.30 ln ms^2) and LF (less than 3.85 ln ms^2) were independent predictors of mortality, with RRs of 2.1 (95% CI 1.1 to 4.0), 2.5 (95% CI 1.2 to 5.1) and 2.2 (95% CI 1.1 to 4.5), respectively, in a sample of 697 MI patients followed for a mean (± SD) period of 18.4±6.5 months. Twenty-four hour nonlinear measures also appear to hold prognostic significance for MI patients (8,15,22,28). Specifically, Kiviniemi et al (26) found that after controlling for ejection fraction, age and diabetes in 590 MI subjects followed for an average of 39 months, reduced V_{index} (less than 4.45 ms^2) was the most powerful independent predictor of sudden cardiac death (RR 4.2; 95% CI 1.2 to 15.2), while an increased prevalence of low-frequency oscillation (0.11 Hz or greater) and diminished α_1 (lower than 0.75) predicted nonsudden cardiac death with RRs of 4.3 (95% CI 1.6 to 11.4) and 5.2 (95% CI 2.2 to 12.3), respectively.

CHF

Abnormalities in 24 h HRV indexes were found to be predictive of poorer outcomes in the CHF population (Table 2). Galinier et al (29) reported that CHF patients with an SDNN of less than 67 ms were at a 2.5-fold increased risk for all-cause mortality and progressive heart failure death (RR 2.5; 95% CI 1.5 to 4.2). Additionally, a lower daytime LF power (less than 3.3 ln ms^2) was found to predict sudden death by 2.8-fold (RR 2.8; 95% CI 1.2 to 8.6) in this population. Several additional research groups have reported that reduced SDNN, SD of 5 min average N-N intervals, variance of all N-N intervals, ULF, LF and α_1 HRV parameters were independent predictors of mortality among individuals with CHF (30-34). Short-term (5 min) controlled breathing LF power (13 ms^2 or less) (RR 3.0; 95% CI 1.2 to 7.6) (35) and LF to high-frequency power (HF)

ratio (hazard ratio 0.8; 95% CI 0.7 to 0.96) (36) were also found to have independent prognostic value for CHF patients at follow-up.

Although it would appear that the short-term and long-term LF spectral components have similar predictive power for CHF patients, there is a greater breadth of evidence in support of the predictive value of 24 h HRV assessment. Specifically, the SDNN parameter appears to hold a great deal of predictive significance among those with CHF. When compared with CHF patients with an SDNN of greater than 100 ms, those with an SDNN of less than 50 ms had an RR of 9.4 (95% CI 4.1 to 20.6) and had a 51.4% annual mortality rate. Those with an SDNN between 50 ms and 100 ms had an RR of 2.4 (95% CI 1.2 to 4.5) and an annual mortality rate of 12.7% (33). Similarly, Bilchick et al (31) found that individuals in the lowest SDNN quartile (65.3 ms or less) were at the greatest risk of all-cause mortality compared with individuals in the higher quartiles (P<0.0001). Interestingly, they also discovered a 20% decrease in mortality risk with each increase of 10 ms in the SDNN parameter (P=0.0001) based on a Cox proportional hazards model.

Unstable angina

HRV may be an independent prognostic determinant for individuals with unstable angina (Table 2). In 2006, Lanza et al (37) reported that an LF of less than 15.6 ms was an independent predictor of in-hospital mortality (OR 4.5; 95% CI 1.0 to 19.7), six-month total mortality (RR 2.2; 95% CI 1.1 to 4.0) and cardiac mortality (RR 2.9; 95% CI 1.3 to 6.5). In another study (38), a trend for a higher LF/HF ratio was found to independently predict an in-hospital event (cardiac death, MI or coronary revascularization) in patients with unstable angina (OR 2.8; 95% CI 0.6 to 15.3).

Coronary artery bypass grafting

Although reduced HRV has been found to be associated with a worse prognosis in several cardiac populations, so far, prospective studies have found HRV assessment to provide no prognostic significance among individuals who have undergone coronary artery bypass grafting (CABG) surgery (39) (Table 2). Stein et al (40) found a similar result in their retrospective analysis of the Cardiac Arrhythmia Suppression Trial (CAST). This suggests that HRV may not be a uniform prognostic indicator in all clinical populations (39). It has been proposed that decreased HRV may be the result of increased sympathetic activity during CABG surgery. However, it is possible that a completely different mechanism is responsible for autonomic denervation in this group (39).

Diabetes mellitus

Impaired autonomic nervous function among patients with diabetes as assessed by HRV has been observed in otherwise healthy adults (41,42), as well as in children (43) and adolescents (41,44). Both short-term (45-47) and 24 h (48,49) assessments have revealed the prognostic significance of HRV among individuals with type 1 and/or type 2 diabetes (Table 2). HRV indexes have been associated with carotid intima-media thickness (49) and progressive renal deterioration (48). Decreased HRV among individuals with diabetes has also been found to be predictive of cardiovascular morbidity and mortality (45-47). Astrup et al (45) found that type 1 diabetic patients with an HRV of 10 beats/min or less had an HR of 4.9 (95% CI 2.1 to 11.5) for fatal and nonfatal cardiovascular events compared with those with a normal HRV of 15 beats/min or more.

In summary, time domain, frequency domain, spectral and nonlinear measures of HRV have been evaluated as a means of predicting short- and long-term outcomes. Overall, evidence suggests that HRV assessment has prognostic significance for individuals with MI, CHF, unstable angina and diabetes such that decreased HRV predicts adverse events and poor outcomes. However, there appears to be no prognostic power associated with HRV assessment in the CABG population.

EXERCISE THERAPY AND HRV MODIFICATION IN CLINICAL POPULATIONS

Exercise therapy has been shown to increase HRV in healthy individuals (50-52). Therefore, exercise training may improve cardiac autonomic regulation in a variety of clinical populations including individuals with MI, HF, CABG, percutaneous transluminal coronary angioplasty (PTCA) and diabetes mellitus. One hypothesis is that physical exercise modulates cardiac autonomic control by lessening sympathetic influence and enhancing vagal tone (53). This shift toward greater vagal modulation may positively affect the prognosis of individuals with a variety of morbidities (53).

MI

Physical exercise is recommended for patients with cardiac disease including those who have experienced an MI. Several researchers have investigated the effects of exercise training on cardiac autonomic functioning in the post-MI population (54) (Table 3). La Rovere et al (55) used head-up tilt testing to evaluate HRV in 22 trained and untrained MI patients. They found that in the trained group, there were significantly greater LF increases (84±3 normalized units [nu] versus 69±5 nu) and HF decreases (7±1 nu versus 19±4 nu) during the head-up tilt test. The normal response to orthostatic stress, such as in the tilt test, is a reduction in vagal tone and an increase in sympathetic vasoconstrictor outflow due to initiation of the baroreceptors (56). Therefore, the findings of this study suggest that trained MI patients' autonomic pathways may be functionally better than MI patients who did not participate in a training program.

Several studies have documented improvements in HRV via participation in exercise training programs among MI patients. Sandercock et al (57) found that following an eight-week cardiac rehabilitation program, 21 male and 17 female participants had significant increases in HRV parameters compared with those not participating in the training program. In another study (58), researchers reported a 25% increase in SDNN, a 69% increase in the square root of the mean of the sum of squares of successive N-N interval differences, a 120% increase in the number of successive N-N intervals differing by more than 50 ms divided by the total number of successive N-N intervals and a 30% reduction in LF/HF ratio after 22 MI patients completed an eight-week endurance rehabilitation program. These improvements continued to be observed at one year following participation in the eight-week training program. In this study (58), participants were also encouraged to continue exercising at home two to three times per week following completion of the formal training program. Comparable improvements in HRV have been reported in studies of MI patients participating in unsupervised low-intensity walking programs as well as more intensive supervised exercise programs (59). It is important to note that the HRV benefits of cardiac rehabilitation have also been observed among MI patients who were hypertensive and normotensive (60). These initial findings suggest that improvements in HRV may be achieved from supervised or unsupervised exercise training programs of variable intensities and durations among MI patients with or without high blood pressure.

Researchers have also reported that a two-week exercise program consisting of two 30 min daily sessions of cycle ergometry at the anaerobic threshold facilitated parasympathetic nervous system activity recovery after an MI more quickly than for those participating in a walking cardiac rehabilitation program (54). Specifically, the delta value of HF was significantly greater for MI patients randomly assigned to the cycle ergometry exercise program compared with individuals participating in the walking program (30±6 ms^2 versus 10±8 ms^2). The cycle ergometry exercise program participants continued to have greater increases in HF (55±8 ms^2 to 106±31 ms^2; P<0.05) than walking program participants (48±6 ms^2 to 66±14 ms^2; P value nonsignificant) when re-evaluated at three months. These findings suggest that anaerobic threshold exercise training may also improve autonomic nervous function among individuals who have experienced an MI. At the same time, interpretations of these results are cautionary given that the walking protocol is described as "a conventional rehabilitation protocol" without inclusion of the exercise program's frequency or duration. In another study (53), the combination of beta-blocker medication along with cardiac rehabilitation in MI patients was found to increase HRV to a greater extent than in individuals only receiving beta-blockers or cardiac rehabilitation.

TABLE 2
Prognostic value of heart rate variability (HRV) among individuals with clinical conditions

Publication	Clinical population	Study design	n (age)	HRV measure	Follow-up	Predictive outcomes*
MI						
Kiviniemi et al (26)	AMI	Prospective	590 (61±10)	24 h Holter monitoring (5–10 d post-AMI)	39±14 mths	After controlling for EF, age and DM: Reduced VLF, LF, α_1 and V_{index} were predictors of all-cause mortality; reduced V_{index} predicted sudden cardiac death, and reduced α_1, PLF; and LF predicted nonsudden cardiac death
Stein et al (8)	MI	Retrospective	749 (61±10)	24 h Holter monitoring (71±120 d post-MI)	362±241 d	Decreased ULF, increased SD12 (nonlinear HRV), history of MI and history of CHF significantly predicted mortality
Balanescu et al (20)	AMI	Prospective	463 (60.6±13)	24 h Holter monitoring (10–20 d post-AMI)	1 yr	Independent predictors of total mortality 1 yr post-MI were reduced SDNN and rMSSD, and LF/HF ratio >2, nonsustained VT, and LVEF <40%
Carpeggiani et al (86)	AMI	Prospective	413 (56±8)	24 h Holter monitoring (48±14 h from admission)	Hospital stay (days not reported)	Decreased LF and family history of ischemic heart disease were the only predictors of major intrahospital events (cardiac death, resuscitated VF, cardiogenic shock, VT, angina and heart failure)
Hohnloser et al (24)	AMI	Prospective	674 (61.5±10.9 in ICD group; 62.1±10.6 in control)	24 h Holter monitoring (≤3 d post-AMI)	30±13 mths	SDNN was not found to be predictive of mortality in high-risk patients with a recent MI in either treatment group (ICD or no ICD)
Steeds et al (23)	AMI	Prospective	137 (62±11 in living; 69±11 in deceased)	Short-term (5 min, 2-lead ECG) recordings (≤48 h of admission)	32 mths (median)	Reduced mean N-N interval was a significant predictor of adverse prognosis and SDNN was an independent predictor of an adverse prognosis until LVEF was included in the model
Stein et al (27)	MI	Retrospective analysis	735 (age not reported)	24 h Holter monitoring (71±120 d post-MI)	362±243 d	Decreased 24 h TP and ULF were the strongest predictors of mortality in the group, excluding individuals with CABG and DM
Wichterle et al (28)	AMI	Retrospective analysis	1139 (57.3±10)	24 h Holter recordings (<28 d post-AMI)	674±234 d	LVEF and PLF ≥0.1 Hz remained independent predictors of the combined end point (cardiac mortality or resuscitated cardiac arrest with VF)
Wichterle et al (28)	AMI	Retrospective analysis	633 (60.7±9.2)	24 h Holter recordings 5–21 d post-AMI	662±105 d	PLF ≥0.1 Hz was the most powerful predictor of all-cause mortality, followed by reduced HF and previous MI
Whang and Bigger (9)	AMI	Retrospective analysis	715 (59±7 with DM; 56±9 no DM)	24 h Holter monitoring (≤2 wks post-AMI)	30 mths	Reduced HRV for TP, ULF, VLF and SDNN were significantly associated with all-cause mortality in DM after adjusting for age, LVEF, heart failure and ventricular arrhythmias, VPC and pulmonary rales
Sosnowski et al (22)	AMI	Prospective	298 (56±10)	24 h ECG (>3 mths post-MI)	24 mths	Reduced HRV fraction and SDNN had a significant predictive value of total mortality and cardiac mortality
Tapanainen et al (15)	AMI	Prospective	697 (61.2±10.1)	24 h portable R-R interval recorder (5–14 d post-AMI)	18.4±6.5 mths	After adjusting for clinical variables and wall-motion index, reduced α_1 was the most powerful predictor of all-cause mortality followed by reduced LF/HF, VLF, β, LF and ULF
La Rovere et al (19)	AMI	Retrospective analysis	1071 (59±10)	24 h Holter monitoring (<28 d post-AMI)	21±8 mths	SDNN (<70 ms) was significantly and independently predictive of a worse cardiac mortality
La Rovere et al (21)	AMI	Retrospective analysis	1284 (57±10)	24 h Holter monitoring (<28 d post-AMI)	21±8 mths	Patients with low SDNN (<70 ms) had higher mortality than those with well-preserved values independent of LVEF and ventricular arrhythmias
Lanza et al (87)	AMI	Prospective	239 (61±11)	24 h Holter monitoring (5–20 d post-AMI)	28 mths (median)	No HRV measures significantly predicted mortality
Bigger et al (88)	AMI	Retrospective	715	24 h Holter monitoring (2 wks post-AMI)	4 yrs	Decreased TP, ULF and VLF remained significant and strongly associated with mortality. LF and HF were moderately strongly associated with mortality
CHF						
Anastasiou-Nana et al (89)	CHF (LVEF <40%)	Prospective	52 (56±12)	24 h ECG recordings	2 yrs	No HRV parameter was a significant predictor of all-cause mortality but reduced HF power was a significant predictor of sudden death
Aronson et al (30)	Hospitalized, CHF (NYHA class III–IV)	Prospective	199 (60±14)	24 h Holter recordings	312±150 d	Decreased SDNN, SDANN, TP and ULF remained independent predictors of mortality. ULF was the single component with the strongest mortality association
La Rovere et al (35)	CHF (NYHA class II–III)	Retrospective	202 (52±9)	Short-term (5 min) ECG recording	3 yrs	Reduced short-term LF (≤13 ms^2) during controlled breathing and LV end-diastolic diameter emerged as independent predictors of sudden death
Bilchick et al (31)	CHF (LVEF <40%; NYHA class II–III)	Retrospective analysis	127 (65±9)	24 h Holter recordings	1 yr	Reduced SDNN was the sole predictor of overall mortality

TABLE 2 – CONTINUED
Prognostic value of heart rate variability (HRV) among individuals with clinical conditions

Publication	Clinical population	Study design	n (age)	HRV measure	Follow-up	Predictive outcomes*
CHF – CONTINUED						
Makikallio et al (32)	Hospitalized CHF (LVEF ≤35%; NYHA class II–IV)	Prospective	499 (alive: 68±10; deceased: 72±8)	24 h ECG recordings (5–10 d after hospitalization)	665±374 d	After adjusting for age, LV wall-motion index, functional class, digoxin, diuretics and creatinine clearance, decreased α_1 remained an independent predictor of mortality. When analyzed according to functional class, decreased α_1 remained a significant predictor for class II but not class III or IV after adjustment for other variables
Galinier et al (29)	CHF (LVEF ≤45%; NYHA class II–IV) Stable for 2 wks	Prospective	190 (61±12)	24 h Holter ECG recordings	22±18 mths	Reduced SDNN was found to have an independent prognostic value for all-cause mortality and progressive heart failure death, and a lower daytime LF for sudden death. An SDNN <67 ms increased the risk of all-cause and progressive heart failure death 2.5-fold; LF during daytime <3.3 ms^2 increased the risk of sudden death 2.8-fold
Lucreziotti et al (36)	CHF (LVEF <35%; NYHA class II–IV)	Prospective	75 (50.5±10.9)	Short-term (5 min) ECG recording	11.4 mths (median)	Decreased LF/HF ratio was found to have a significant and independent prognostic value. Frequency of events (cardiac death, heart transplant) was significantly higher in pts with LF/HF <0.70 than in pts with LF/HF ≥0.7
Nolan et al (33)	CHF (NYHA class I–III)	Prospective	433 (62±9.6)	24 h ECG recordings	482±161 d	Reduced SDNN, cardiothoracic ratio, LVESD and sodium were significantly associated with all-cause mortality
Ponikowski et al (34)	CHF (NYHA class II–IV)	Prospective	102 (58±10)	24 h ECG recordings	584±405 d	Reduced SDNN, SDANN and LF were predictors of cardiac death independently of peak oxygen consumption, NYHA class, EF and VT
Unstable angina						
Lanza et al (6)	Unstable angina (LVEF ≥40%)	Prospective	543 (65.2±10)	24 h ECG Holter monitoring within 24 h of hospitalization	6 mths	Reduced LF power was consistently found to be independently associated with fatal end points (total and cardiac deaths at 6 mths after adjusting for age, sex, cardiac risk factors and history of MI)
Lanza et al (38)	Unstable angina	Prospective	75 (62±9)	24 h ECG Holter monitoring within 12 h of hospitalization	In-hospital	Increased LF/HF was just above statistical significance (P=0.08) for independent predictor of major cardiac events (cardiac death, acute MI, coronary revascularization) among pts with transient myocardial ischemia
CABG						
Milicevic et al (39)	CABG and MI	Prospective	51 (CABG 56±11) 127 (MI 64±9)	24 h Holter monitoring	46±20 mths	HRV has no prognostic value in CABG pts. Deceased MI pts had lower SDNN than those who survived the follow-up period
DM						
Astrup et al (45)	Type 1 DM	Prospective	197 (DM and nephropathic; 41±9), 191 (DM; 43±10)	Short-term expiration/ inspiration HRV. Supine breathing at 6 respiratory cycles for 1 min while being monitored by ECG	10.1 yrs	A decrease in HRV was found to be a significant independent predictor of cardiovascular morbidity or mortality among type 1 diabetic pts with nephropathy
Gottsater et al (49)	Type 2 DM	Prospective	61 (median 59; range 45–69)	24 h ECG monitoring	8 yrs	Pts with a lower LF power during the day at baseline had a larger increase in the thickness of the carotid bulb intima-media at follow-up (correlational analysis)
Kataoka et al (46)	Type 2 DM	Prospective	3089 (DM; 60.1±7.2), 5828 (non-DM; 59.6±7)	100 successive R-R intervals measured in a 12-lead ECG	6.5±4.8 yrs	In DM pts, only age, CV r-r (<2.2%) and smoking history remained statistically significant risk factors for sudden cardiac death
Burger et al (48)	Type 1 DM	Prospective	23 (37±10)	24 h ECG recordings at baseline and 12 mths	1 yr	Reduced SDNN, SDANN, pNN50, rMSSD and LF were significant and independent predictors of abnormalities in creatinine clearance (progressive renal deterioration) at 1 yr
Wheeler et al (47)	DM (types 1 and 2)	Prospective	843 (deceased 66.6±8.9; living 62.1±10.0)	Short-term HRV analysis. Pt supine, breathing at 6 respiratory cycles/min: R-R variability was measured with a ruler	42.4 mths (mean)	Lower HRV was found to be an independent risk factor for mortality in diabetic pts followed in a primary care setting

*Age presented as mean (± SD) years. Follow-up data presented as mean ± SD unless otherwise indicated. *Multivariate analysis unless otherwise stated. Refer to Table 1 for descriptions of α_1, β, HF, LF, PLF, pNN50, rMSSD, SD12, SDANN, SDNN, TP, ULF, V_{index} and VLF. AMI Acute myocardial infarction; CABG Coronary artery bypass grafting surgery; CHF Chronic heart failure; CV r-r Coefficient of variation of 100 successive r-r intervals; d Days; DM Diabetes mellitus; ECG Electrocardiogram; EF Ejection fraction; ICD Implantable cardioverter defibrillator; LV Left ventricle; LVEF LV ejection fraction; LVESD LV end-systolic diameter; MI Myocardial infarction; mths Months; N-N Normal R wave to R wave (R-R) interval; NYHA New York Heart Association; pts Patients; VF Ventricular fibrillation; VPC Ventricular premature complexes; VT Ventricular tachycardia; wks Weeks; yr Year*

TABLE 3
Heart rate variability (HRV) modification via exercise therapy among individuals with clinical conditions

Publication	Clinical population	n (age)	HRV assessment	Exercise therapy and duration	HRV outcome
MI					
Sandercock et al (57)	MI, CABG, angioplasty	CR group: 38 (65.6±11.6) Control group: 23 (64.9±9)	Short-term (5 min) supine ECG recordings at baseline and at 8 wks	8-wk CR program: 1.5 h of aerobic exercise	Compared with the control group, the CR group had significant increases in SDNN, HF (ln), LF (ln) and R-R interval
Oya et al (54)	MI*	Training group: 16 (59±7) Control group: 12 (58±7)	Short-term ECG recordings during rest, warmup and exercise at wk 1, wk 3 and mth 3 post-MI	Started wk 1 post-MI. Training group: 30 min of cycle ergometer at anaerobic threshold 2×/d for 2 wks. Control group: Walking according to CR protocol for 2 wks	HF increased in both groups. Increase was only significant in the training group from wks 1 to 3. There were no significant differences in HF when comparing the training and control groups from 3 wks to 3 mths
Malfatto et al (53)	MI	CR-only group: 14 (52±2) CR + BB group: 20 (53±2) BB-only group: 14 (53±3)	Short-term ECG (15–20 min) supine at 3–4 wks post-MI, after completing 8 wks of CR and 1 yr after MI	Started 4 wks post-MI; 8 wks endurance training,1 h session of calisthenics and bicycle exercise 5 d/wk. Exercise schedule given at CR discharge	4 wks after MI, patients taking BB had greater HRV (higher RRSD, MSSD, pNN50). 8 wks following CR, increases in MSSD and pNN50, and decreases in LF/HF were observed with greater changes observed in the BB + CR group. Effects maintained at 1 yr post-MI. BB-only group: HRV did not change over time
Leitch et al (59)	MI	Training group: 26 (56±1) Control group: 23 (59±1)	24 h Holter monitoring 5–7 d post-MI and at 6 wks (after 5 d medication washout period)	Started 7–10 d post-MI. Training group: 6 wks supervised moderate-intensity hospital-based exercise training program (leg ergometry and circuit training) 30–60 min 3–4×/wk. Control group: Unsupervised low-intensity walking program (5–30 min 2×/d)	In both groups, there were significant improvements in all measures of HRV (mean R-R, SDNN, SDANN, TP, LF, HF). There were no significant differences between groups in any HRV parameter
Bryniarski et al (60)	MI	HTN group: 34 (52±9.4) Normotensive group: 30 (52±9.7)	24 h ECG monitoring at baseline and following exercise program	4-wk supervised program: 5×/wk, including gymnastics 20 min 2×/d; bicycle ergometer 3×/wk for 30–45 min; jogging 2×/wk for 1.5 km	CR increased all HRV indexes (SDNN, SDANN index, SDNN index, rMSSD, pNN50) in both groups. There were no differences between hypertensive or normotensive post-MI patients who had CR
Malfatto et al (58)	MI	Training group: 22 (52±7) Control group: 8 (53±7)	Short-term (15 min) resting ECG recordings at 4 wks, 3 mths and 1 yr post-MI	8 wks of endurance training: 1 h of calisthenics and stationary cycling 5×/wk. Exercise encouraged 2–3×/wk at discharge	At 3 mths post-MI, the trained pts showed significant increases in R-R, RRSD, MSSD, pNN50 and HF, as well as lower LF and LF/HF. No significant changes were observed in the untrained group. Differences were maintained at 1 yr in the trained group
La Rovere et al (55)	MI	Total = 22 Trained group: (47±6) Control group: (54±10)	Short-term (15 min) ECG recordings during resting and 70º tilt, and 24 h ECG recordings at 4 and 8 wks post-MI	4-wk in-hospital physical training program of calisthenics and bicycle ergometery at 75% to 95% of anaerobic threshold	At baseline, both groups had a predominantly LF component and a smaller HF component with no further modification after head-up tilt. After 4 wks, no resting changes were observed in HRV in either group. During head-up tilt, the trained group had significantly greater LF component increases and HF component decreases
Mazzuero et al (61)	Anterior MI	Training group: 22 Control group: 16 (50±8)	24 h ECG recording during drug washout period at 4–6 wks and 6 mths post-MI	6-mth training program. Training group: 30 min bicycle ergometry 3×/wk. Control group: Free lifestyle of choice	24 h HRV (SDNN and LF/HF) increased from the 2nd to 8th mth postanterior MI, independently of exercise training or ejection fraction
CHF					
Selig et al (67)	CHF (LVEF <40%, NYHA class II–III)	Exercise therapy group: 19 (65±13) Control group: 20 (64±9)	Short-term (20 min supine) ECG recording	Supervised hospital 3-mth program; 3×/wk of multistation hydraulic resistance training, leg cyclic ergometers and set of 5 stairs	Exercise therapy group: After 3 mths, there were significant changes in the HRV parameters. LF and LF/HF decreased, HF increased. No changes were observed in the control group. Mean R-R, SDNN and rMSSD were not different in either group
Malfatto et al (65)	CHF (mean NYHA class 2.7, mean LVEF 30%)	CR group: 30 (62±7) Control: 15 (60±16)	Short-term (10 min) ECG recordings after 10 min of supine rest and free breathing; 10 min of regular breathing at 20 acts/min; 10 min active standing	Supervised hospital-based 3-mth ambulatory rehabilitation; low-intensity training, 1 h of calisthenics, treadmill or bicycle 5×/wk. At discharge, encouraged to continue training program at home 2–3×/wk	After 3 mths of exercise: LF/HF at rest was unchanged, significant decreased LF/HF with controlled breathing and increased LF/HF during standing compared with baseline and free breathing in the rehabilitation group. Changes were greater after 6 additional mths of home-based training. No changes in control group

TABLE 3 - CONTINUED
Heart rate variability (HRV) modification via exercise therapy among individuals with clinical conditions

Publication	Clinical population	n (age)	HRV assessment	Exercise therapy and duration	HRV outcome
CHF – CONTINUED					
Pietila et al (66)	CHF (LVEF 36%, NYHA class II–III)	13 (58.2±7.1)	Short-term (5 min) ECG recordings at supine rest at baseline and 6 mths	6-mth home-based exercise program; 30 min of walking, step-board exercise, ergometer or other aerobic exercise 1×/d, 6 d/wk	Following the 6 mths of training, the HF and total R-R interval variability significantly increased
Kiilavuori et al (64)	CHF (LVEF <40%; NYHA class II–III)	Exercise group: 8 (52±8) Control group: 12 (52±10)	20 h ECG recordings (12:00–08:00 h) at baseline and 3 mths	Supervised hospital-based 3-mth training program; 30 min bicycle ergometer 3×/wk	Training group: After 3 mths of exercise, HF during the day increased and 24 h HF increased. No changes in the control group. LF/HF ratio lower during the day and nonsignificant trend for lower 24 h LF/HF ratio in exercise group. Significant increase in the LF/HF ratio during the day and at night for the control group
PTCA and CABG					
Tsai et al (71)	PTCA	84 (57.0±9.3)	Short-term (5 min, supine) ECG recordings at baseline and at the end of 8 wks	Supervised outpatient and home exercise program for 8 wks (bicycle ergometer)	In the exercise group, HF power increased 10%, mean R-R interval increased 5% and there was a 5% increase in the variance in the exercise group, whereas in the control group, there were decreases in these HRV indexes
Lucini et al (69)	Post major IHD event (CABG, MI, PTCA)	CR group: 29 (63±1.97) Control group: 11 (53±2.38)	Short-term (10 min supine) ECG recordings at baseline, 4 wks and following exercise program	12 wks of 36 educational and exercise sessions. 50–60 min of stretching, calisthenics, aerobic and dynamic exercise (walking, bicycling, jogging, rowing), and hand weights. Encouraged to exercise 1–3×/wk outside of the formal program	After exercise therapy, the R-R interval variance increased significantly in the exercise group
Iellamo et al (68)	CABG	Training group: 45 (59.4±7.8) Untrained group: 41 (58.5±7.3)	Short-term (10 min supine) at baseline and after 2-wk training period	Residential exercise program; 2×/d, 6×/wk for 2 wks, 30 min of stationary cycling and calisthenics	Mean R-R interval and the R-R interval significantly increased in the training group after 2 wks of exercise therapy
Takeyama et al (70)	CABG	Training group: 13 (60.4±7.8) Control group: 15 (61.7±8.7)	Short-term recordings at 1 wk, 3 wks, and 3, 6 and 12 mths following surgery	All pts attended CR 1 wk after surgery. Training group: 30 min cycle ergometry 2×/d for 2 wks. Control group: Instructed to walk 200–500 m 3×/d for 2 wks	At rest, HF increased significantly from baseline at 3 mths, 6 mths and 12 mths in both groups. There was no significant difference between the groups. During constant load exercise, HF increased significantly in the training group at wk 3 and at 3 mths in the control group. The increases were smaller in the control group at all measurement points. At 3, 6 and 12 mths, the HF increases during constant load exercise were greater in the training group
DM					
Figueroa et al (72)	Obese women with and without type 2 DM	With DM: 10 (50±1) Without DM: 18 (48±2)	Short-term (5 min supine) before and after 20 min of exercise	16 wks moderate-intensity endurance training: Supervised home-based walking program, 4 d/wk for 30–45 min	Postexercise HF and LF significantly increased in both groups by 14% after 16 wks of exercise. No differences in HRV between groups following exercise training
Zoppini et al (73)	Type 2 DM	12 (65.7±5.6)	Short-term (10 min, supine and standing) ECG recordings at baseline and 6 mths	6-mth exercise program: Moderate, aerobic exercise program for 70 min 2×/wk	Standing position: HF increased, LF decreased and LF/HF ratio decreased after exercise. There were no significant changes in HRV parameters in the supine position
Loimaala et al (74)	Men with type 2 DM	Exercise group: 24 (53.6±6.2) Control group: 25 (54.0±5.0)	24 h ECG recordings	52-wk training program: Jog or walk, and muscle strength training 2×/wk, along with conventional treatment for DM. Control group: Conventional treatment for DM only	Nonstatistically significant trend toward higher SDNN, HF and LF in the training group for the sleep values compared with the control group. HRV measures did not change between or within the study groups

*Age presented as mean (± SD) years. *Patients with myocardial infarction (MI) undergoing conventional therapy, angioplasty or revascularization. Refer to Table 1 for descriptions of HF, LF, pNN50, rMSSD, SDANN, SDNN and TP. BB Beta-blocker; CABG Coronary artery bypass grafting; CHF Chronic heart failure; CR Cardiac rehabilitation; d day; DM Diabetes mellitus; ECG Electrocardiogram; HTN Hypertension; IHD Ischemic heart disease; LVEF Left ventricular ejection fraction; MSSD The mean of the sum of squared differences between R-R intervals; mth Month; NYHA New York Heart Association; pts Patients; PTCA Percutaneous transluminal coronary angioplasty; RRSD The standard deviation of mean R-R interval; wk Week; yr Year*

This finding suggests a potentially favourable interaction between physical training and antiadrenergic pharmacotherapy (53).

Although most studies have reported positive findings, one study found that improved HRV among MI patients was independent of exercise training (61). However, the researchers noted that a relatively high baseline HRV combined with a low-intensity training program and lack of activity monitoring in the control group may have impacted the results (61). Thus, findings to date generally lend support to the notion that exercise therapy positively modifies HRV in MI patients.

CHF

CHF is characterized by inadequate cardiac function, and is associated with reduced exercise tolerance (62) and HRV (63). Exercise training has been found to have beneficial effects on HRV in this clinical

population (64-66) (Table 3). Malfatto et al (65) reported greater restoration of autonomic nervous system responsiveness to vagal and sympathetic stimulation in CHF patients who completed three months of low-intensity exercise therapy. After three months of low-intensity physical training (in which HR reached 40% to 50% of peak oxygen consumption), the LF/HF ratio at rest remained unchanged, but there was an 18% reduction in LF/HF ratio during controlled breathing (20 breaths/min; vagal stimulus) and a 79% increase in LF/HF after standing (10 min duration; sympathetic stimulus). These changes were more evident after six months of additional home-based training. Interestingly, it has been suggested that CHF patients may require more time to achieve modulation of autonomic tone and responsiveness than MI patients. This may be due, in part, to the chronic nature of heart failure, which may contribute to greater autonomic impairment (65).

Improvements in HRV among CHF patients have also been observed in supervised aerobic exercise programs (64), supervised resistance training programs (67) and home-based training programs (66). These findings suggest that a variety of exercise therapy programs may be used to progress toward greater HRV in the CHF population.

Angioplasty, CABG and unstable angina

Among patients with coronary artery disease who have undergone PTCA or CABG, exercise therapy has been found to significantly increase various indexes of HRV (68-71) (Table 3). These findings suggest that analysis of HRV can be used to assess the effect of exercise training on cardiac autonomic dysfunction in this population. However, as previously mentioned, the predictive value of HRV in the CABG population remains to be demonstrated. In addition, we are unaware of exercise therapy studies of HRV among individuals with unstable angina.

Diabetes mellitus

Several studies have examined the effect of exercise on HRV in patients with diabetes. Following participation in an exercise program, postexercise HF increased by 14% in 28 obese women with and without type 2 diabetes (72). Autonomic function did not differ between the two groups following exercise training, suggesting that there may be no additional benefit of exercise on HRV among obese women with type 2 diabetes. Zoppini et al (73) discovered that standing HF increased, and LF and LF/HF ratio decreased significantly in type 2 diabetic patients following a six-month exercise program of 70 min of moderate aerobic exercise twice weekly. It should be noted that this study did not include a control group. Loimaala et al (74) reported no differences in the time domain or frequency domain HRV measures in 24 men with type 2 diabetes who participated in an exercise training program. Additionally, there were no significant differences reported between the exercise and control groups (Table 3). Therefore, the findings to date are inconclusive with respect to the idea that exercise may improve parasympathetic regulation of heart rate among individuals with diabetes.

In summary, regular physical activity is known to reduce a person's risk of morbidity and mortality from a variety of diseases (75). The findings of the present review suggest that exercise therapy may improve HRV in MI, CHF, PTCA and CABG patients by increasing vagal tone and decreasing sympathetic activity. One hypothesis is that a shift toward greater vagal modulation may positively affect prognosis of individuals with a variety of morbidities (53). Furthermore, speculation could be made that there is a potential reduction in mortality and morbidity related to HRV change in patients who exercise.

POTENTIAL MECHANISMS IN THE MODIFICATION OF HRV BY EXERCISE THERAPY

Enhanced cardiac vagal tone may offer a survival advantage. Greater vagal influence decreases the amount of work and oxygen consumed by the heart via a reduction in resting heart rate and myocardial contractility (76). It appears that stimulation of the vagus nerve directly acts on the sinus node and the myocardium, and hinders sympathetic influences (76-78). Cardiac vagal tone may also reduce the risk of frequently lethal ventricular dysrhythmias including ventricular fibrillation (76).

Exercise training may enhance vagal tone and thereby decrease susceptibility to lethal arrhythmias (76). While the underlying mechanisms by which exercise training improves vagal modulation are speculative at present, angiotensin II and nitric oxide (NO) are potential mediators.

A potential mechanism underlying the exercise training-cardiac vagal tone association is angiotensin II. Angiotensin II is known to inhibit cardiac vagal activity (79). One theory is that exercise training suppresses angiotensin II expression (76). Researchers have also discovered that plasma renin activity levels are lower in athletes (long-distance runners) than in untrained individuals or nonathletes (80) and sedentary individuals (81). This finding is important given that athletes with lower plasma renin activity would presumably have lower angiotensin II and higher associated levels of cardiac vagal activity. Therefore, it is possible that the suppression of angiotensin II via exercise may, to some extent, mediate enhancement of cardiac vagal tone (76).

NO may also play a role in increasing cardiac vagal control and, in doing so, may indirectly inhibit sympathetic influences (82). Exercise training has been found to improve endothelial function (83) and NO bioavailability (84) among individuals with coronary risk or coronary atherosclerosis. Therefore, it is possible that the relationship between exercise and cardiac vagal activity is mediated, at least in part, by NO. However, more research is needed to clarify the possible role of NO in autonomic control (82) as well as its potential influence on the exercise-cardiac vagal tone relationship (76).

Limited research to date suggests that exercise training (endurance training in particular) increases cardiac vagal tone and reduces sympathetic cardiac influences (85). The exact mechanisms underlying the modification of HRV by exercise therapy are not known. Angiotensin II and NO have been proposed as potential mediators in this relationship. However, more research is required to substantiate these claims, particularly with respect to NO.

CONCLUSION

Research findings suggest that decreased HRV is a prognostic indicator in individuals with a variety of clinical conditions. Research findings also suggest that depressed vagal cardiac modulation may contribute to adverse outcomes (68). A variety of supervised and unsupervised exercise therapy programs of variable intensities have increased HRV in individuals with cardiovascular diseases and diabetes. However, the mechanisms mediating the beneficial modification of HRV by exercise therapy are not known. Some evidence suggests that angiotensin II and NO may play mediating roles. Overall, the findings to date imply that exercise therapy exerts its influence on HRV via increasing vagal modulation and decreasing sympathetic tone. Further research is needed to identify the exercise regimen (ie, duration and intensity) that produces optimal improvements in HRV. Research is also needed to evaluate whether exercise interventions are effective long-term therapies for stimulating favourable autonomic nervous system alterations and producing meaningful improvements in outcomes in clinical populations.

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