ORIGINAL ARTICLE

Double Product and Autonomic Function as Predictors of Quality of Life in Heart Transplant Recipients: A Cross-Sectional Study

Luiz Fernando Rodrigues Junior¹,², PT; Beatriz Robert Moreira¹, PT; Alice Pereira Duque¹, MD; Juliana Rega de Oliveira¹, PT; Pedro Henrique Scheidt Figueiredo³, PT; Cláudia Rosa de Oliveira¹, PT; Alexandre Siciliano Colafranceschi³, MD; Mauro Felippe Felix Mediano¹,³, PT; Tereza Cristina Felippe Guimarães³, RN

ABSTRACT

Introduction: Heart rate control by the autonomic nervous system (ANS) is impaired in heart transplant (HT) recipients, leading to increased resting heart rate, metabolic demand, and fatigue, which can impair their quality of life (QoL). In this study, we hypothesized the association of hemodynamics and autonomic function as predictors of QoL in HT recipients.

Methods: This is a cross-sectional study conducted with HT recipients aged ≥ 18 years at ambulatorial accompaniment. Blood pressure was used for hemodynamics assessment, and heart rate variability (HRV) was used for ANS assessment. QoL was assessed by the 36-item Short Form Health Survey. The significance level was set as \( P \leq 0.05 \).

Results: Twenty-two volunteers were included in the study. Systolic blood pressure (SBP) and double product (DP) were significantly negatively associated with the physical functioning domain of QoL. DP, the number of consecutive normal RR interval differences > 50 ms (NN50), and the percentage of normal RR intervals that differed by > 50 ms from the adjacent interval (PNN50) exhibited negative association with the physical role domain. NN50 and PNN50 were significantly associated with bodily pain, social functioning, and emotional role domains. SBP was negatively associated with the vitality domain. Considering general and mental health domains, no variable demonstrated significant association. DP, NN50, and PNN50 were negatively associated with the total score of QoL.

Conclusion: This study demonstrated DP and HRV as predictors of QoL in HT recipients. These innovative results can become a relevant therapeutic target for improving QoL in HT recipients prior to its deterioration.

Keywords: Heart Transplantation. Quality Of Life. Autonomic Nervous System. Heart Rate Variability. Hemodynamics.

Abbreviations, Acronyms & Symbols

| ANS                  | = Autonomic nervous system |
|----------------------|---------------------------|
| BP                   | = Blood pressure          |
| CI                   | = Confidence interval     |
| DBP                  | = Diastolic blood pressure|
| DP                   | = Double product          |
| HF                   | = High frequency component|
| HR                   | = Heart rate              |
| HRV                  | = Heart rate variability  |
| HT                   | = Heart transplant        |
| LF                   | = Low frequency component |
| LF/HF                | = Low frequency/high frequency ratio (sympathovagal index) |
| MAP                  | = MeWan arterial pressure |
| NN50                 | = Number of consecutive normal RR interval differences > 50 ms |
| PANS                 | = Parasympathetic autonomic nervous system |
| PNN50                | = Percentage of normal RR intervals that differed by > 50 ms from the adjacent interval |
| QoL                  | = Quality of life         |
| RMSSD                | = Root-mean-square of successive differences |
| SANS                 | = Sympathetic autonomic nervous system |
| SBP                  | = Systolic blood pressure |
| SD                   | = Standard deviation      |
| SD1                  | = Standard deviation of instantaneous beat-to-beat interval variability |
| SD2                  | = Continuous long-term RR interval variability |
| SDNN                 | = Standard deviation of normal RR interval |
| SF-36                | = 36-item Short Form Health Survey |
| TINN                 | = Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals |

¹Physiotherapy Service, Instituto Nacional de Cardiologia, Rio de Janeiro, Rio de Janeiro, Brazil.
²Department of Physiological Sciences, Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro, Brazil.
³Education and Research Department, Instituto Nacional de Cardiologia, Rio de Janeiro, Rio de Janeiro, Brazil.
⁴Postgraduate Program in Rehabilitation and Functional Performance, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, Minas Gerais, Brazil.
⁵Laboratory of Clinical Research on Chagas Disease, Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Rio de Janeiro, Brazil.

This study was carried out at the Education and Research Department, Instituto Nacional de Cardiologia, Rio de Janeiro, Rio de Janeiro, Brazil.

Correspondence Address:
Luiz Fernando Rodrigues Junior
https://orcid.org/0000-0001-7007-7431
Edson Teixeira Filho, Instituto Nacional de Cardiologia
Rua das Laranjeiras, 374, Bairro das Laranjeiras, Rio de Janeiro, RJ, Brazil
Zip Code: 22240-006
E-mail: luiz.junior@unirio.br

DOI: 10.21470/1678-9741-2021-0083

Article received on February 8th, 2021.
Article accepted on December 9th, 2021.
INTRODUCTION

Heart failure — the final stage of most heart diseases and the main cause of death of patients with ischemic heart disease in the United States of America and other Western countries — is characterized by the inability of the heart to provide adequate blood supply to all tissues of the body, impairing patients’ functional capacity and quality of life (QoL). As the disease advances further, morbidity and mortality increase. Therapeutic refractory heart failure necessarily culminates in death, being heart transplant (HT) the only alternative to avoid this outcome. This treatment has immeasurable benefits such as prolonging survival by approximately 10 years following surgery and also improving symptoms of heart failure, enabling a more active lifestyle and improving QoL for the 85% of individuals that survive the first year after HT surgery.

However, during surgical procedure, transplanted hearts are implanted without afferent and efferent nerve connections, remaining completely denervated for approximately one year. Consequently, heart rate (HR) control by the autonomic nervous system (ANS) is impaired, leading to increased resting HR, increased metabolic demand, and fatigue, which can negatively impact QoL of HT recipients due physiological, clinical, and behavioral profile impairments, such as the need for more daily-use medications for HR controlling. Usually, there are evidence of reinnervation occurring in the second year after surgery, reaching myocardial muscle, sinoatrial node, and coronary vessels, but remaining incomplete and regionally limited many years after the transplant. Nevertheless, restoration of cardiac innervation can improve exercise capacity as well as blood flow regulation in the coronary arteries, and hence improve QoL.

In the present study, we hypothesized the association of hemodynamics and autonomic function as predictors of QoL in HT recipients, which could be future monitoring and therapeutic target for improving QoL of this population.

METHODS

Study Design

This is a cross-sectional study conducted from January to July 2017 using baseline data from a previously published clinical trial. All patients in ambulatorial accompaniment after heart transplantation at the Instituto Nacional de Cardiologia were eligible for the study. After phone contact, those ≥ 18 years old who accepted to participate were included, and those not able to presently respond the questionnaires were excluded from the study.

Ethical Considerations

This study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. The Ethics Committee of the Instituto Nacional de Cardiologia approved the study, and all patients signed an informed consent form before the beginning of the data collection.

Measurements

All the information was collected in person, after ambulatorial medical appointment, on individual assessment sheets filled out by the same researcher previously trained to perform all the study procedures. The following data were collected: age, gender, history of previous and current disease, comorbidities, and QoL. Assessments of HR, blood pressure (BP), and heart rate variability (HRV) were also performed.

QoL Assessment

The Portuguese validated version of 36-item Short Form Health Survey (SF-36) was used to assess health-related QoL. The SF-36 is divided in eight dimensions: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. Also, the summary Physical Composite Score (comprising physical functioning, physical role, bodily pain, and general health) and Mental Composite Score (comprising vitality, social functioning, emotional role, and mental health) were calculated and used to obtain the total QoL score, representing the mean value of the Physical and Mental Composite Scores. The scores ranged from 0 to 100, with higher values denoting better functioning and well-being.

Heart Rate, Blood Pressure, and Heart Rate Variability Measurements

The resting HR, BP, and HRV measurements were carried out in a quiet room with a controlled temperature (23°C). HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were registered after a 20-minute resting period, in the sequence of the interview, and anthropometric measurements were obtained with the patients at supine position. BP, HR, and RR interval were registered. The double product (DP) was calculated as a product of HR and SBP.

The RR intervals were continuously recorded throughout a 10-minute period after resting using a HR monitor (RS800; Polar, United States of America) and subsequently used to evaluate HRV using appropriate software (Kubios v.2.2; University of Eastern Finland, Finland). The sympathetic autonomic nervous system (SANS) and parasympathetic autonomic nervous system (PANS) activity were quantified using HRV by calculating the following time-domain parameters: mean of all normal RR interval (mean RR, associated to SANS and PANS modulations), standard deviation of normal RR interval (or SDNN, associated to activity of both SANS and PANS), number of consecutive normal RR interval differences > 50 ms (NN50, associated to the PANS activity), percentage of normal RR intervals that differed by > 50 ms from the adjacent interval (PNIN50, the proportion of NN50 divided by total number of NN, which also represents the PANS activity), root-mean-square of successive differences (or RMSSD, associated to the PANS activity), triangular index (total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 7.8125 ms [1/128 seconds]), and the baseline width of the minimum square difference triangular interpolation of the highest peak of
the histogram of all NN intervals (or TINN). Also, the integration of the successive HR bands was classified in relation to the frequency domain as follows: very low frequency component (0.003–0.04 Hz; related to renin-angiotensin-aldosterone system, thermoregulation, peripheral vasomotor tonus, and PANS activity), low frequency component (LF; 0.04–0.15 Hz; representing the SANS and PANS activity, with a predominance of SANS influence), and high frequency component (HF; 0.15–0.4 Hz; associated with the PANS activity). The ratio of LF to HF (LF/HF) was used to calculate the sympathovagal index. The normalized power of the LF and HF components (representing total HRV) was calculated in standard units (nu). Finally, nonlinear analysis of HRV was made using the Poincaré plot to calculate the standard deviation of instantaneous beat-to-beat interval variability (SD1, associated to the PANS activity), the continuous long-term RR interval variability (SD2, representing total HRV), and the SD1/SD2 ratio (SD12) [12,13].

Data Analysis

Descriptive analysis consisted of mean and standard deviation (SD) for continuous variables and percentage and number of observations for categorical variables. The association between the variables was determined using linear regression models with each QoL domain (functional capacity, physical aspects, pain, general health status, vitality, social aspects, emotional aspects, mental health, and total score) as the dependent variable, and the physiological measurements (HR, SBP, DBP, MAP, DP, HRV variables) as independent variables. Models were fitted without adjustments and adjusted for age, gender, and time since surgery, considering the role of these variables as potential confounders. The P-value < 0.05 was considered statistically significant.

RESULTS

A total of 22 volunteers were included in the study, five women (22.7%) and 17 men (77.3%), with mean age of 53.4 (9.3) years old. The HT indications were: chagasic cardiomyopathy, myocarditis, ischemic heart disease, and valvar dysfunction due to rheumatic disease, each with four cases (18.2%); and alcoholic, idiopathic, and peripartum cardiomyopathy with three (3.7%), two (9.1%), and one case (4.5%), respectively. Also, the mean time since surgery was 4.3 (2.5) years. The main comorbidities were hypertension (50.0%), diabetes (31.8%), obesity (27.2%), dyslipidemia (22.7%), hypothyroidism (13.7%), chronic kidney disease (13.7%), and hyperthyroidism (4.5%).

Table 1 shows the crude means and SD of hemodynamics, the time, frequency, and nonlinear domains of HRV, and QoL domains of the studied sample. The non-adjusted association analysis is presented in Tables S1 and S2.

The associations of hemodynamics and HRV with QoL domains are depicted in Tables 2 and 3. SBP and DP were negatively associated with the physical functioning domain (Table 2). DP, NNS50, and PNN50 exhibited negative association with the physical role domain (Table 2), while only NNS50 and PNN50 were significantly associated with bodily pain (Table 2), social functioning, and emotional role domains (Table 3). For the vitality domain (Table 3), only SBP was negatively associated. Considering general (Table 2) and mental health (Table 3) domains, none of hemodynamic or HRV variables demonstrated significant association. Finally, DP, NNS50, and PNN50 were negatively associated with the total score of QoL (Table 4).

DISCUSSION

The main finding of the present study was the negative association of hemodynamic and autonomic function indexes with QoL in HT recipients. The benefits of heart transplantation for health-related QoL are well described for several domains/areas such as physical, psychological, and social [14–16] but the role of hemodynamic and autonomic function variables as predictors of QoL has never been previously described. Briefly, the main variables exhibiting its association were SBP, DP, NNS50, and PNN50.

Considering hemodynamics, the higher the SBP, the worse the physical function and vitality domains of QoL. Both elevated BP and total peripheral resistance and also attenuated BP and total peripheral resistance responses during orthostatic maneuvers are observed in HT recipients, probably due low-pressure cardiopulmonary baroreceptor denervation. Moreover, efferent sympathetic denervation leads to diminished cardiac output response to isometric exercise after heart transplantation. Together, those physiological impairments impose negative functional consequences to HT recipients [17] that could explain the observed negative association of SBP with domains of QoL. In addition, as observed in the present study, the higher the DP, the worse the physical function and physical role domains of QoL. As an index of myocardial oxygen consumption previously used during exercise testing in patients with coronary heart disease, DP reflects cardiac workload, being a well-established index of energy consumption of heart [18]. Therefore, increases in DP at rest could indicate a small DP reserve (difference between rest and maximal exercise DP) that has greater prognostic power than metabolic equivalents, maximal HR, or SBP [19], reflecting the efficiency of the myocardium [20]. Then, elevated resting DP could impair physical function — and by consequence, the clinical status of those patients — due to elevated resting myocardial oxygen consumption and low exercise capacity by reduced cardiac reserve [21], worsening QoL.

Considering autonomic function, NNS50 and PNN50 (indexes associated with parasympathetic activity [22], more reliable in short-term observations [23]) increases were contradictorily associated with reduction of physical role, bodily pain, social functioning, and emotional role domains and total score. PNN50 was already correlated to decreases in physical function [24].

Despite the expected improvement in QoL due to increased parasympathetic activation, that could ameliorate hemodynamics by reducing resting HR, SBP, and finally DP; improving DP reserve and, as consequence, cardiac reserve and exercise capacity, which would result in clinical improvements, it was not demonstrated in the present study. Since parasympathetic fibers only innervate nodal pacemakers’ cells, the main influence of its activation should be the stimulation of HR reduction, or more precisely, the inhibition of HR elevation due to humoral adrenergic stimulation [25,26].
Table 1. Baseline characteristics of patients included in the study.

| Variable                  | Mean ± SD or Number (%) |
|---------------------------|-------------------------|
| **Hemodynamics**          |                         |
| HR (bpm)                  | 78.8±6.9                |
| SBP (mmHg)                | 124.6±11.9              |
| DBP (mmHg)                | 84.0 (7.3)              |
| MAP (mmHg)                | 101.0 (10.0)            |
| DP (bpm.mmHg)             | 9802.9±1104.2           |
| **HRV**                   |                         |
| **Time domain**           |                         |
| Mean RR (ms)              | 769.6±71.6              |
| SDNN (ms)                 | 7.2±3.0                 |
| RMSSD (ms)                | 6.1±3.4                 |
| NN50 (number)             | 0.1±0.3                 |
| PNN50 (%)                 | 0.2±0.1                 |
| Triangular index          | 2.5±0.7                 |
| TINN (ms)                 | 28.6±19.6               |
| **Frequency domain**      |                         |
| Total power (ms²)         |                         |
| VLF (ms²)                 | 34.4±45.3               |
| LF (nu)                   | 37.6±22.5               |
| HF (nu)                   | 61.4±21.4               |
| LF/HF                     | 0.9±0.7                 |
| **Nonlinear**             |                         |
| SD1                       | 3.8±2.3                 |
| SD2                       | 9.4±3.9                 |
| SD1/SD2 ratio             | 0.4±0.2                 |
| **Quality of life (SF-36)**|                       |
| Physical functioning      | 77.9±21.7               |
| Physical role             | 78.4±41.0               |
| Bodily pain               | 72.8±30.2               |
| General health            | 64.6±15.4               |
| Vitality                  | 74.1±23.4               |
| Social functioning        | 86.4±16.8               |
| Emotional role            | 93.9±16.7               |
| Mental health             | 77.8±16.7               |
| Physical health composite | 73.44±21.6              |
| Mental health composite   | 83.0±14.2               |
| Total score               | 78.2±17.5               |

DBP=diastolic blood pressure; DP=double product; HF=high frequency component; HR=heart rate; HRV=heart rate variability; LF=low frequency component; LF/HF=low frequency/high frequency ratio (sympathovagal index); MAP=mean arterial pressure; NN50=number of consecutive normal RR interval differences > 50 ms; PNN50=percentage of normal RR intervals that differed by > 50 ms from the adjacent interval; RMSSD=root-mean-square of successive differences; SBP=systolic blood pressure; SD=standard deviation; SD1=standard deviation of instantaneous beat-to-beat interval variability; SD2=continuous long-term RR interval variability; SDNN=standard deviation of normal RR interval; SF-36=36-item Short Form Health Survey; TINN=baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals; VLF=very low frequency component.
Table 2. Associations of hemodynamics and heart rate variability variables with SF-36 Physical Composite domains.

|                      | Physical Functioning | Physical Role | Bodily Pain | General Health |
|----------------------|----------------------|---------------|-------------|----------------|
|                      | β        | 95% CI | P-value | β        | 95% CI | P-value | β        | 95% CI | P-value | β        | 95% CI | P-value |
| **Hemodynamics**     |          |        |         |          |        |         |          |        |         |          |        |         |
| HR (bpm)             | -0.2     | -1.6 to +1.2 | 0.758 | -1.6     | -4.2 to 1.0 | 0.201 | -0.9     | -3.0 to +1.1 | 0.355 | +0.1     | -0.1 to +1.0 | 0.954 |
| SBP (mmHg)           | -0.6     | -1.3 to 0.0 | 0.050 | -0.6     | -2.0 to +0.7 | 0.343 | -0.8     | -1.8 to +0.2 | 0.126 | -0.1     | -0.6 to +0.4 | 0.724 |
| DBP (mmHg)           | -0.2     | -1.4 to 0.9 | 0.681 | -1.0     | -3.2 to 13.9 | 0.326 | -1.0     | -2.6 to +0.7 | 0.234 | -0.1     | -0.8 to +0.8 | 0.947 |
| MAP (mmHg)           | -0.6     | -1.6 to 0.4 | 0.248 | -1.0     | -2.9 to +0.9 | 0.293 | -1.1     | -2.5 to +0.4 | 0.145 | -0.1     | -0.8 to +0.7 | 0.835 |
| DP (bpm.mmHg)        | -0.1     | -0.1 to 0.0 | 0.045 | -0.1     | -0.1 to 0.0 | 0.006 | -0.1     | -0.1 to +0.1 | 0.171 | 0.0      | 0.0 to +0.1 | 0.989 |
| **HRV**              |          |        |         |          |        |         |          |        |         |          |        |         |
| **Time domain**      |          |        |         |          |        |         |          |        |         |          |        |         |
| Mean RR (ms)         | +0.1     | -0.2 to +0.1 | 0.315 | +0.1     | -0.2 to +0.4 | 0.671 | -0.1     | -0.3 to +0.1 | 0.461 | -0.1     | -0.1 to +0.1 | 0.428 |
| SDNN (ms)            | +1.1     | -3.2 to 5.4 | 0.595 | +1.0     | -7.3 to +9.4 | 0.794 | -0.4     | -7.0 to +6.1 | 0.888 | -0.2     | -3.4 to +2.7 | 0.846 |
| RMSSD (ms)           | +0.3     | -3.1 to 3.8 | 0.829 | -1.0     | -34.2 to +663 | 0.766 | -1.5     | -6.7 to +3.7 | 0.544 | +0.9     | -1.5 to +3.3 | 0.438 |
| NN50 (number)        | -29.4    | -62.2 to +3.3 | 0.075 | -95.4    | -145.4 to -45.4 | 0.001 | -62.4    | -106.8 to -18.0 | 0.009 | +1.3     | -24.4 to +27.0 | 0.916 |
| PNN50 (%)            | -108.7   | -229.6 to +12.2 | 0.075 | -352.0   | -536.5 to -67.5 | 0.001 | -230.3   | -394.1 to -66.4 | 0.009 | +4.8     | -90.0 to +99.7 | 0.916 |
| Triangular index     | +5.0     | -12.0 to +22.0 | 0.545 | +15.8    | -16.6 to +48.2 | 0.318 | -1.9     | -28.0 to +24.2 | 0.882 | -4.1     | -16.2 to +8.0 | 0.484 |
| TINN (ms)            | +0.1     | -0.5 to +0.7 | 0.667 | +0.2     | -1.0 to +1.3 | 0.752 | -0.1     | -0.9 to +0.9 | 0.980 | +0.3     | -0.4 to +0.4 | 0.885 |
| **Frequency domain** |          |        |         |          |        |         |          |        |         |          |        |         |
| Total power (ms²)    | +0.1     | -0.2 to +0.2 | 0.697 | 0.0      | -0.4 to +0.5 | 0.827 | -0.1     | -0.4 to +0.3 | 0.817 | -0.1     | -0.2 to +0.1 | 0.326 |
| VLF (ms²)            | +0.1     | -0.2 to +0.3 | 0.609 | +0.2     | -0.3 to +0.7 | 0.411 | +0.1     | -0.4 to +0.4 | 0.957 | -0.1     | -0.3 to +0.1 | 0.073 |
| LF (nu)              | -0.1     | -0.6 to +0.3 | 0.684 | -0.1     | -1.0 to +0.8 | 0.795 | +0.1     | -0.6 to +0.8 | 0.867 | -0.1     | -0.5 to +0.2 | 0.444 |
| HF (nu)              | +0.1     | -0.4 to +0.6 | 0.674 | +0.1     | -0.9 to +10.0 | 0.899 | -0.1     | -0.9 to +0.6 | 0.729 | +0.1     | -0.2 to +0.5 | 0.432 |
| LF/HF                | -3.0     | -17.2 to +11.2 | 0.663 | -1.6     | -30.8 to 65.6 | 0.456 | +1.7     | -19.9 to +23.4 | 0.866 | -4.1     | -14.1 to +5.9 | 0.397 |
| **Nonlinear**        |          |        |         |          |        |         |          |        |         |          |        |         |
| SD1                  | +0.8     | -3.8 to +5.4 | 0.707 | -1.7     | -10.6t +7.2 | 0.692 | -2.6     | -9.5 to +4.3 | 0.438 | +1.7     | -1.5 to +4.9 | 0.281 |
| SD2                  | +1.5     | -2.3 to +5.2 | 0.419 | +3.4     | -3.9 to +10.7 | 0.335 | +1.5     | -4.3 to +7.3 | 0.585 | -0.4     | -3.1 to +2.3 | 0.765 |
| SD1/SD2              | +2.1     | -4.18 to +46.1 | 0.919 | -2.34    | -107.7 to +609 | 0.566 | -2.67    | -92.0 to +38.5 | 0.399 | 15.9     | -143.0 to +46.2 | 0.282 |

Statistical analysis was adjusted for age, gender, and time since surgery.
CI = confidence interval; DBP = diastolic blood pressure; DP = double product; HF = high frequency component; HR = heart rate; HRV = heart rate variability; LF = low frequency component; LF/HF = low frequency/high frequency ratio (sympathovagal index); MAP = mean arterial pressure; NN50 = number of consecutive normal RR interval differences > 50 ms; PNN50 = percentage of normal RR intervals that differed by > 50 ms from the adjacent interval; RMSSD = root-mean-square of successive differences; SBP = systolic blood pressure; SD1 = standard deviation of instantaneous beat-to-beat interval variability; SD2 = continuous long-term RR interval variability; SDNN = standard deviation of normal RR interval; SF-36 = 36-item Short Form Health Survey; TINN = baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals; VLF = very low frequency component.
Table 3. Associations of hemodynamics and heart rate variability variables with SF-36 Mental Composite domains.

|                      | Vitality | Social Functioning | Emotional Role | Mental Health |
|----------------------|----------|--------------------|----------------|--------------|
|                      | β        | 95% CI             | P-value        | β            | 95% CI     | P-value | β            | 95% CI     | P-value | β            | 95% CI     | P-value |
| **Hemodynamics**     |          |                    |                |              |            |         |              |            |         |              |            |         |
| HR (bpm)             | +0.3     | -1.1 to +1.9       | 0.684          | -0.7        | -1.7 to +0.4 | 0.207   | -0.3        | -1.4 to +0.7 | 0.501   | -0.1        | -1.3 to +1.0 | 0.793   |
| SBP (mmHg)           | -0.7     | -1.5 to +0.1       | 0.047          | -0.2        | -0.7 to +0.4 | 0.504   | -0.3        | -0.8 to +0.3 | 0.328   | -0.3        | -0.9 to +0.3 | 0.354   |
| DBP (mmHg)           | -0.7     | -1.9 to +0.6       | 0.280          | -0.5        | -1.4 to +0.4 | 0.243   | -0.4        | -1.3 to +0.4 | 0.305   | +0.1        | -0.9 to +1.0 | 0.907   |
| MAP (mmHg)           | -0.9     | -2.0 to +0.2       | 0.110          | -0.4        | -1.2 to +0.4 | 0.304   | -0.4        | -1.2 to +0.4 | 0.275   | -0.1        | -1.0 to +0.7 | 0.715   |
| DP (bpm:mmHg)        | -0.1     | -0.1 to +0.1       | 0.277          | -0.1        | -0.1 to +0.1 | 0.172   | -0.1        | -0.1 to +0.1 | 0.210   | -0.1        | -0.1 to +0.1 | 0.849   |
| **HRV**              |          |                    |                |              |            |         |              |            |         |              |            |         |
| Time domain          |          |                    |                |              |            |         |              |            |         |              |            |         |
| Mean RR (ms)         | -0.1     | -0.2 to +0.1       | 0.153          | +0.1        | -0.1 to +0.1 | 0.797   | -0.1        | -0.1 to +0.1 | 0.651   | -0.1        | -0.2 to +0.1 | 0.560   |
| SDNN (ms)            | -0.6     | +5.5 to +43        | 0.787          | -1.0        | -4.4 to +2.4 | 0.525   | -1.1        | -4.4 to +2.2 | 0.495   | +1.6        | -1.9 to +5.1 | 0.343   |
| RMSSD (ms)           | +0.8     | -2.7 to +4.4       | 0.632          | -0.4        | -3.2 to +2.3 | 0.736   | -2.0        | -4.5 to 0.5  | 0.104   | +1.9        | -0.9 to +4.6 | 0.168   |
| NN50 (number)        | -18.4    | -58.5 to +21.7     | 0.346          | -36.0       | -58.0 to -14.0 | 0.003  | -48.2       | -62.0 to -34.4 | <0.001 | -8.4        | -38.4 to +21.6 | 0.562  |
| PNN50 (%)            | -68.0    | -215.9 to +80.0    | 0.346          | -132.7      | -213.9 to -51.5 | 0.003  | -178.0      | -228.8 to -27.1 | <0.001 | -31.0       | -141.6 to +79.6 | 0.562  |
| Triangular index     | -8.1     | -27.3 to +11.2     | 0.388          | +0.6        | -13.1 to +14.3 | 0.923   | -0.4        | -13.9 to +13.1 | 0.956   | +4.3        | -10.0 to +18.6 | 0.537   |
| TINN (ms)            | +0.1     | -0.6 to +0.8       | 0.781          | -0.1        | -0.5 to +0.5  | 0.933   | -0.1        | -0.5 to +0.4  | 0.731   | +0.2        | -0.2 to +0.7  | 0.300   |
| Frequency domain     |          |                    |                |              |            |         |              |            |         |              |            |         |
| Total power (ms²)    | -0.1     | -0.4 to +0.1       | 0.410          | -0.1        | -0.2 to +0.1 | 0.589   | -0.1        | -0.2 to +0.1 | 0.567   | +0.1        | -0.1 to +0.2 | 0.686   |
| VLF (ms²)            | -0.5     | -0.2 to +0.1       | 0.167          | -0.2        | -0.2 to +0.2 | 0.861   | +0.1        | -0.1 to +0.2 | 0.581   | -0.1        | -0.2 to +0.2 | 0.837   |
| LF (nu)              | -0.2     | -0.8 to +0.2       | 0.258          | -0.1        | -0.5 to +0.3 | 0.592   | -0.1        | -0.4 to +0.4 | 0.972   | -0.2        | -0.6 to +0.1 | 0.203   |
| HF (nu)              | +0.3     | -0.3 to +0.8       | 0.332          | +0.1        | -0.3 to +0.5 | 0.725   | -0.1        | -0.4 to +0.4 | 0.987   | +0.2        | -0.2 to -0.6 | 0.252   |
| LF/HF                | -7.2     | -23.1 to +8.7      | 0.354          | -1.6        | -13.0 to +9.7 | 0.764   | -0.8        | -12.1 to +10.3 | 0.868   | -6.4        | -18.0 to +5.1 | 0.257   |
| Nonlinear            |          |                    |                |              |            |         |              |            |         |              |            |         |
| SD1                  | +0.6     | -4.6 to +5.9       | 0.791          | -0.7        | -4.4 to +2.9 | 0.680   | -2.7        | -9.6 to +0.7 | 0.110   | +2.1        | -1.6 to +5.9 | 0.251   |
| SD2                  | -0.7     | -5.1 to +3.7       | 0.725          | -0.2        | -3.2 to +3.0 | 0.940   | +0.1        | -2.9 to +3.1 | 0.929   | +1.7        | -1.4 to +4.8 | 0.268   |
| SD1/SD2              | +14.1    | -35.6 to +63.8     | 0.557          | -4.7        | -39.5 to +30.2 | 0.781   | -26.3       | -58.1 to +53.0 | 0.097   | +13.5       | -22.7 to +49.8 | 0.441   |

Statistical analysis was adjusted for age, gender, and time since surgery.

CI=confidence interval; DBP=diastolic blood pressure; DP=double product; HF=high frequency component; HR=heart rate; HRV=heart rate variability; LF=low frequency component; LF/HF=low frequency/high frequency ratio (sympathovagal index); MAP=mean arterial pressure; NN50=number of consecutive normal RR interval differences > 50 ms; PNN50=percentage of normal RR intervals that differed by > 50 ms from the adjacent interval; RMSSD=root-mean-square of successive differences; SBP=systolic blood pressure; SD1=standard deviation of instantaneous beat-to-beat interval variability; SD2=continuous long-term RR interval variability; SDNN=standard deviation of normal RR interval; SF-36=36-item Short Form Health Survey; TINN=baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals; VLF=very low frequency component.
### Table 4. Associations of hemodynamics and heart rate variability variables with SF-36 total score.

| Variable            | β    | 95% CI       | P-value   |
|---------------------|------|--------------|-----------|
| **Hemodynamics**    |      |              |           |
| HR (bpm)            | -0.4 | -1.6 to +0.7 | 0.434     |
| SBP (mmHg)          | -0.4 | -1.0 to +0.1 | 0.118     |
| DBP (mmHg)          | -0.5 | -1.4 to +0.5 | 0.307     |
| MAP (mmHg)          | -0.6 | -1.4 to +0.3 | 0.172     |
| DP (bpm.mmHg)       | -0.1 | -0.1 to -0.0 | 0.039     |
| **HRV**             |      |              |           |
| **Time domain**     |      |              |           |
| Mean RR (ms)        | -0.1 | -0.2 to +0.1 | 0.569     |
| SDNN (ms)           | 0.1  | -3.7 to +3.7 | 0.985     |
| RMSSD (ms)          | -1.26| -3.1 to +2.9 | 0.929     |
| NN50 (number)       | -37.1| -61.6 to -12.6 | 0.005    |
| PNN50 (%)           | -137.0| -227.3 to -46.7 | 0.005 |
| Triangular index    | +1.4 | -13.4 to +16.2 | 0.843 |
| TINN (ms)           | +0.1 | -0.4 to +0.6 | 0.777     |
| **Frequency domain**|      |              |           |
| Total Power (ms²)   | -0.1 | -0.2 to +0.2 | 0.805     |
| VLF (ms²)           | -0.1 | -0.2 to +0.2 | 0.946     |
| LF (nu)             | -0.1 | -0.5 to +0.3 | 0.563     |
| HF (nu)             | +0.1 | -0.3 to +0.5 | 0.662     |
| LF/HF               | -2.9 | -15.1 to +9.3 | 0.624 |
| **Nonlinear**       |      |              |           |
| SD1                 | -0.3 | -4.3 to +3.7 | 0.874     |
| SD2                 | +0.9 | -2.4 to +4.2 | 0.581     |
| SD1/SD2             | -4.4 | -42.1 to +33.3 | 0.807 |

Statistical analysis was adjusted for age, gender, and time since surgery.

CI=confidence interval; DBP=diastolic blood pressure; DP=double product; HF=high frequency component; HR=heart rate; HRV=heart rate variability; LF=low frequency component; LF/HF=low frequency/high frequency ratio (sympathovagal index); MAP=mean arterial pressure; NN50=number of consecutive normal RR interval differences > 50 ms; PNN50=percentage of normal RR intervals that differed by > 50 ms from the adjacent interval; RMSSD=root-mean-square of successive differences; SBP=systolic blood pressure; SD1=standard deviation of instantaneous beat-to-beat interval variability; SD2=continuous long-term RR interval variability; SDNN=standard deviation of normal RR interval; SF-36=36-item Short Form Health Survey; TINN=baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals; VLF=very low frequency component.
Table S1. Associations between hemodynamics and heart rate variability variables with SF-36 Physical Composite domains (non-adjusted analysis).

| Physical role | Physical functioning | Hemodynamics | β | 95% CI | P-value | β | 95% CI | P-value | β | 95% CI | P-value | β | 95% CI | P-value | β | 95% CI | P-value |
|---------------|----------------------|--------------|----|--------|---------|----|--------|---------|----|--------|---------|----|--------|---------|----|--------|---------|
| HR (bpm)      |                      |              | -0.4 | (1.5, -0.0) | 0.404 | -1.6 | (-3.6, 0.0) | 0.397 | +0.1 | (0.0, 0.2) | 0.100 | +0.7 | (0.6, 0.8) | 0.572 | +0.1 | (0.0, 0.2) | 0.808 |
| SBP (mmHg)    |                      |              | -0.7 | (-1.3, -0.1) | 0.019 | -1.0 | (-2.1, 0.1) | 0.177 | +0.1 | (0.0, 0.2) | 0.966 | -0.2 | (-0.4, 0.0) | 0.725 | -0.2 | (-0.4, 0.0) | 0.957 |
| MAP (mmHg)    |                      |              | -0.6 | (-1.6, 0.4) | 0.101 | -2.0 | (-4.0, 0.0) | 0.290 | +0.1 | (0.0, 0.2) | 0.906 | +0.1 | (0.0, 0.2) | 0.725 | +0.1 | (0.0, 0.2) | 0.808 |
| DBP (mmHg)    |                      |              | -0.1 | (-0.2, 0.0) | 0.247 | -0.2 | (-0.4, 0.0) | 0.128 | +0.1 | (0.0, 0.2) | 0.112 | -0.1 | (-0.2, 0.0) | 0.200 | -0.1 | (-0.2, 0.0) | 0.091 |
| MAP (mmHg)    |                      |              | +0.2 | (0.1, 0.3) | 0.008 | -0.1 | (-0.2, 0.0) | 0.208 | -0.1 | (-0.2, 0.0) | 0.168 | +0.1 | (0.0, 0.2) | 0.557 | +0.1 | (0.0, 0.2) | 0.557 |
| HRV Time domain |                    |              |      |          |         |      |          |         |      |          |         |      |          |         |      |          |         |
| Mean RR (ms)  |                      |              | +0.1 | (-0.1, 0.3) | 0.247 | -0.2 | (-0.4, 0.0) | 0.128 | +0.1 | (0.0, 0.2) | 0.112 | -0.1 | (-0.2, 0.0) | 0.200 | -0.1 | (-0.2, 0.0) | 0.168 |
| SDNN (ms)     |                      |              | +2.3 | (2.0, 2.6) | 0.003 | -1.8 | (-3.6, 0.0) | 0.102 | +0.2 | (0.0, 0.4) | 0.041 | +0.1 | (0.0, 0.2) | 0.725 | +0.1 | (0.0, 0.2) | 0.808 |
| RMSSD (ms)    |                      |              | +1.2 | (1.0, 1.4) | 0.003 | -1.8 | (-3.6, 0.0) | 0.102 | +0.2 | (0.0, 0.4) | 0.041 | +0.1 | (0.0, 0.2) | 0.725 | +0.1 | (0.0, 0.2) | 0.808 |
| NN50 (number) |                      |              | 0.25 | (0.0, 0.5) | 0.003 | -1.8 | (-3.6, 0.0) | 0.102 | +0.2 | (0.0, 0.4) | 0.041 | +0.1 | (0.0, 0.2) | 0.725 | +0.1 | (0.0, 0.2) | 0.808 |
| PNN50 (%)     |                      |              |      |          |         |      |          |         |      |          |         |      |          |         |      |          |         |
| Triangular index |                  |              | +1.8 | (1.5, 2.0) | 0.003 | -1.8 | (-3.6, 0.0) | 0.102 | +0.2 | (0.0, 0.4) | 0.041 | +0.1 | (0.0, 0.2) | 0.725 | +0.1 | (0.0, 0.2) | 0.808 |
| SD1           |                      |              |      |          |         |      |          |         |      |          |         |      |          |         |      |          |         |
| SD1/SD2       |                      |              |      |          |         |      |          |         |      |          |         |      |          |         |      |          |         |
| CI=confidence interval; DBP=systolic blood pressure; DP=double product; HF=high frequency component; HR=heart rate; HRV=heart rate variability; LF=low frequency component; LF/HF=low frequency/high frequency ratio (sympathovagal index); MAI=mean arterial pressure; NNI=number of consecutive normal RR interval differences; NN50=number of consecutive normal RR interval differences > 50 ms; pNN50=percentage of normal RR intervals that differed by > 50 ms from the adjacent interval; RMSSD=root-mean-square of successive differences; SBP=systolic blood pressure; SD1=standard deviation of instantaneous beat-to-beat interval variability; SD2=continuous long-term RR interval variability; SD1/SD2=SD1/SD2 ratio; SDNN=standard deviation of normal RR interval variability; SL=standard deviation of instantaneous beat-to-beat interval variability; TINN=baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of normal RR intervals; VLF=very low frequency component
Table S2. Associations between hemodynamics and heart rate variability variables with SF-36 Mental Composite domains (non-adjusted analysis).

|                      | Vitality     | Social functioning | Emotional role | Mental health |
|----------------------|--------------|--------------------|----------------|---------------|
| **Hemodynamics**     |              |                    |                |               |
| HR (bpm)             | +0.3         | -0.8 to +1.5       | 0.536          | -0.5          | -1.3 to +0.3 | 0.215          | -0.4          | -1.3 to +0.4 | 0.281          | -0.1          | -1.0 to +0.7 | 0.723          |
| SBP (mmHg)           | -0.6         | -1.31 to +0.1      | 0.075          | -0.3          | -0.8 to +0.2 | 0.283          | -0.3          | -0.8 to +0.2 | 0.220          | -0.2          | -0.7 to +0.3 | 0.345          |
| DBP (mmHg)           | -0.6         | -1.7 to +0.6       | 0.306          | -0.5          | -1.3 to +0.3 | 0.186          | -0.4          | -1.3 to +0.4 | 0.279          | +0.1          | -0.8 to +0.9 | 0.877          |
| MAP (mmHg)           | -0.8         | -1.8 to +0.3       | 0.138          | -0.5          | -1.2 to +0.2 | 0.184          | -0.4          | -1.2 to +0.3 | 0.210          | -0.1          | -0.9 to +0.6 | 0.721          |
| DP (bpm.mmHg)        | -0.1         | -0.2 to 0.0        | 0.179          | -0.1          | -0.1 to +0.1 | 0.199          | -0.1          | -0.1 to +0.1 | 0.403          | -0.1          | -0.1 to +0.1 | 0.082          |
| **HRV Time domain**  |              |                    |                |               |
| Mean RR (ms)         | -0.1         | -0.2 to +0.1       | 0.202          | +0.1          | -0.1 to +0.1 | 0.625          | -0.1          | -0.1 to +0.1 | 0.660          | -0.1          | -0.1 to +0.1 | 0.534          |
| SDNN (ms)            | -0.6         | -1.1 to +3.1       | 0.759          | -0.1          | -2.7 to +2.5 | 0.935          | -0.4          | -3.0 to +2.2 | 0.757          | +1.0          | -1.5 to +3.5 | 0.419          |
| RMSSD (ms)           | +1.0         | -2.0 to +1.0       | 0.490          | -0.1          | -2.5 to +2.6 | 0.871          | -1.7          | -3.9 to +0.5 | 0.126          | +1.5          | -0.8 to +3.8 | 0.181          |
| NN50 (number)        | -12.7        | -49.4 to +23.9     | 0.477          | -33.1         | -54.8 to -11.5| 0.005          | -48.3         | -62.2 to -34.4| <0.001         | -8.6          | -34.8 to +17.6| 0.502          |
| PNN50 (%)            | -47.0        | -182.3 to +88.3    | 0.477          | -122.2        | -202.1 to -42.4| 0.005          | -178.3        | -229.6 to -127.1| <0.001         | -31.7         | -128.5 to +65.0| 0.502          |
| Triangular index     | -7.2         | -23.1 to +8.7      | 0.357          | +2.8          | -8.8 to +14.4 | 0.620          | +1.1          | -10.4 to +12.7 | 0.840          | +3.3          | -8.2 to +14.8 | 0.553          |
| TINN (ms)            | +0.1         | -0.4 to +0.7       | 0.647          | +0.1          | -0.4 to +0.4 | 0.859          | -0.1          | -0.5 to +0.3 | 0.584          | +0.2          | -0.2 to +0.6 | 0.387          |
| **Frequency domain** |              |                    |                |               |
| Total power (ms²)    | -0.1         | -0.3 to +0.1       | 0.325          | -0.1          | -0.1 to +0.1 | 0.987          | -0.1          | -0.1 to +0.1 | 0.987          | +0.1          | -0.1 to +2   | 0.673          |
| VLF (ms²)            | -0.2         | -0.4 to +0.1       | 0.112          | +0.1          | -0.1 to +0.2 | 0.755          | +0.1          | -0.1 to +0.2 | 0.334          | -0.1          | -0.2 to +0.2 | 0.872          |
| LF (nu)              | -0.3         | -0.7 to +0.1       | 0.186          | +0.1          | -0.3 to +0.3 | 0.995          | +0.1          | -0.2 to +0.4 | 0.760          | -0.1          | -0.5 to +0.1 | 0.201          |
| HF (nu)              | +0.3         | -0.2 to +0.8       | 0.235          | -0.1          | -0.3 to +0.3 | 0.876          | -0.1          | -0.4 to +0.3 | 0.695          | +0.2          | -0.1 to +0.5 | 0.256          |
| LF/HF                | -8.1         | -22.1 to +6.0      | 0.247          | +0.5          | -9.9 to +11.0| 0.917          | +1.0          | -9.4 to +11.4| 0.845          | -5.7          | -15.7 to +4.4 | 0.252          |
| **Non-linear**       |              |                    |                |               |
| SD1                  | +0.9         | -3.7 to +5.6       | 0.676          | -0.4          | -3.8 to +2.9 | 0.798          | -2.7          | -5.7 to +0.4 | 0.087          | +1.8          | -1.5 to +5.0 | 0.270          |
| SD2                  | -0.6         | -3.6 to +2.4       | 0.698          | +0.4          | -1.7 to +2.6 | 0.684          | +0.4          | -1.8 to +2.5 | 0.719          | +0.9          | -1.2 to +3.0 | 0.377          |
| SD1/SD2              | +18.1        | -2.70 to +63.3     | 0.413          | -6.1          | -38.8 t +26.7| 0.704          | -30.2         | -59.8 to -0.7 | 0.045          | +11.7         | -20.6 to +440 | 0.459          |

CI=confidence interval; DBP=diastolic blood pressure; DP=double product; HF=high frequency component; HR=heart rate; HRV=heart rate variability; LF=low frequency component; LF/HF=low frequency/high frequency ratio (sympathovagal index); MAP=mean arterial pressure; NN50=number of consecutive normal RR interval differences > 50 ms; pNN50=percentage of normal RR intervals that differed by > 50 ms from the adjacent interval; RMSSD=root-mean-square of successive differences; SBP=systolic blood pressure; SD1=standard deviation of instantaneous beat-to-beat interval variability; SD2=continuous long-term RR interval variability; SD1/SD2=SD1/SD2 ratio; SDNN=standard deviation of normal RR interval; SF-36=36-item Short Form Health Survey; TINN=baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals; VLF=very low frequency component.
In fact, parasympathetic influence on HR is absent in the majority of patients up to eight years after cardiac transplantation[27], as are in the population of the present study, in which mean time since transplantation was near four years. Furthermore, HR exhibited no association with QoL domains. A possible explanation to such contradiction could be the peripheral effect of parasympathetic nerve stimulation by releasing the neurotransmitter acetylcholine on muscular and endothelial layers of blood vessels, that induces smooth muscle cells contraction, leading to increase of peripheral resistance that, at last, increases SBP[29]. It can be demonstrated by the impairment of cardiac performance during exercise in orthotopic HT recipients, in which acute beta-adrenergic blockade accentuates the impairment in ventricular performance and appears to be detrimental in these patients, probably by reduction in myocardial contractility and increase in peripheral resistance[27]. Thus, this pathophysiological mechanism evidences the impact of ANS imbalance (previously indicating both parasympathetic and sympathetic activation[29]) on physical and emotional functions, which can worse social interactions. Finally, the elevated adrenergic stimulation and plasma circulating catecholamine levels, already associated to pain syndromes via adrenergic receptors stimulation, are suggested in HT recipients[29,30], being a possible mechanism underlining the inverse association of parasympathetic activation and bodily pain QoL domain[31].

Beyond physiological, laboratorial, or clinical variables and morbidities, mortality, and other classical medical hard outcomes, QoL — which reflects “the individual’s perception of their insertion in life, in the context of the culture and value systems in which a person lives and in relation to their goals, expectations, standards and concerns” — is a major outcome for patients’ life, so the majority of healthcare assistance treatment strategy should be focused on its improvement, ensuring that the treatment is centered on the patient rather than the disease[32,33].

However, in clinical practice, it is not easy to assess QoL, mainly because its subjectivity, but also the complexity of health-related QoL questionnaires, and the difficulty for some patients in understanding and answering it. So, based on the results, the main implication for practice was the identification of some hemodynamic and autonomic variables associated with QoL, which may provide a less subjective way for corroborate the interpretation of this relevant outcome, and finally improve clinical management. Despite the need for more research about those associations, maybe the clinical approach of those variables should impact in improvement in QoL for HT patients. So, as noninvasive, cheap, and easy to perform, HRV — a promising tool for clinically monitoring of autonomic dysfunction prior to several cardiovascular disease occurrence and also for monitoring cardiovascular disease progression[34,35] — together with hemodynamic basic measurements, such as BP and DP, could be more than an instrument for ambulatory clinical follow-up, perhaps being added as clinical therapeutic targets for improving QoL (the main objective of heart transplantation), as suggested by our results.

**Limitations**

We consider a study limitation the small sample size and the lack of follow-up of those patients to understand temporal evolution of this association. We are also aware that this is a single-center study, and our results may not apply to other settings.

**CONCLUSION**

The present study demonstrated DP and HRV as predictors of QoL in HT recipients. These innovative results can become a relevant therapeutic target for improving QoL in HT recipients prior to its deterioration.

**ACKNOWLEDGEMENTS**

We would like to thank the researchers from the Undergraduate Program in Cardiovascular Sciences of the Instituto Nacional de Cardiologia for the intellectual support.

**No financial support. No conflict of interest.**

---

**Authors’ Roles & Responsibilities**

| Author | Role and Responsibility |
|--------|-------------------------|
| LFRJ   | Substantial contributions to the conception or design of the work; and the acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published |
| BRM    | Substantial contributions to the conception or design of the work; and the acquisition, analysis, and interpretation of data for the work; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published |
| APD    | Drafting the work and revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published |
| JRO    | Substantial contributions to the conception or design of the work; and the acquisition, analysis, and interpretation of data for the work; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published |
PHSF Drafting the work and revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published

CRO Drafting the work and revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published

ASC Drafting the work and revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published

MFFM Substantial contributions to the conception or design of the work; and the acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published

TCFG Substantial contributions to the conception or design of the work; and the acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published

REFERENCES

1. Albuquerque DC, Neto JD, Bacal F, Rohde LE, Bernardes-Pereira S, Berwanger O, et al. I Brazilian registry of heart failure - clinical aspects, care quality and hospitalization outcomes. Arq Bras Cardiol. 2015;104(6):433-42. Erratum in: Arq Bras Cardiol. 2015;105(2):208. doi:10.5935/abc.20150031.

2. Agnetti G, Piepoli MF, Siniscalchi G, Nicolini F. New insights in the diagnosis and treatment of heart failure. Biomed Res Int. 2015;2015:265260. doi:10.1155/2015/265260.

3. Emini A, Rogers CA, Banner NR, Steering Group, UK Cardiothoracic Transplant Audit. Quality of life of advanced chronic heart failure: medical care, mechanical circulatory support and transplantation. Eur J Cardiothorac Surg. 2016;50(2):269-73. doi:10.1093/ejcts/ezv054.

4. Nicolini F, Piepoli MF, Agnetti G, Siniscalchi G. Alternatives to transplantation in the treatment of heart failure: new diagnostic and therapeutic insights. Biomed Res Int. 2015;2015:278163. doi:10.1155/2015/278163.

5. Harris C, Cao C, Croce B, Munkholm-Larsen S. Heart transplantation. Ann Cardiothorac Surg. 2018;7(1):1-2. doi:10.21037/acs.2018.01.11.

6. Bacal F, Neto JD, Fiorelli AL, Meija J, Marcondes-Braga FG, Mangini S, et al. II Diretriz Brasileira de Transplante Cardíaco [II Brazilian Guidelines for Cardiac Transplantation]. Arq Bras Cardiol. 2010;94(Suppl):e16-76.

7. Verani MS, Nishimura S, Mahmarian JJ, Hays JT, Young JB. Cardiac function after orthotopic heart transplantation: response to postural changes, exercise, and beta-adrenergic blockade. J Heart Lung Transplant. 1994;13(2):181-93.

8. Grupper A, Gewitz H, Kushwaha S. Reinnervation post-heart transplantation. Eur Heart J. 2018;39(20):1799-806. doi:10.1093/eurheartj/ehw694.

9. Moreira BR, Duque AP, Massolar CS, de Lima Pimentel R, Mediano MFS, Guimarães TCF, et al. Transcutaneous electrical stimulation of PCs and PC6 acupoints modulates autonomic balance in heart transplant patients: a pilot study. J Acupunct Meridian Stud. 2019;12;3(4):84-9. doi:10.1016/j.jams.2019.04.001.

10. Campolina AG, Bortoluzzo AB, Ferraz MB, Ciconelli RM. Validação da versão brasileira do questionário genérico de qualidade de vida short-form 6 dimensions (SF-6D Brasil). Cien Saude Colet. 2011;16;7:3103-10. doi:10.1590/s1413-8123201100080010.

11. Pekmezović T, Ješmenica-Lukić M, Petrović T, Spiča V, Tomić A, Kostić VS. Quality of life in patients with progressive supranuclear palsy: one-year follow-up. J Neurol. 2015;262(9):2042-8. doi:10.1007/s00415-015-7815-3.

12. Kim HG, Cheon EJ, Bae DS, Lee YH, Koo BH. Stress and heart rate variability: a meta-analysis and review of the literature. Psychiatry Investig. 2018;15(3):235-45. doi:10.10373/pi.2017.08.17.

13. Roy B, Ghatak S. Nonlinear methods to assess changes in heart rate variability in type 2 diabetic patients. Arq Bras Cardiol. 2013;101(4):317-27. doi:10.5935/abc.20130181.

14. Grady KL. Quality of life after heart transplantation: are things really better? Curr Opin Cardiol. 2003;18(2):129-35. doi:10.1097/00001573-200303000-00011.

15. Grady KL, Jalowiec A, White-Williams C. Quality of life 6 months after heart transplantation compared with indicators of illness severity before transplantation. Am J Crit Care. 1998;7(2):106-16.

16. Trevisan ME, Porto AS, Pinheiro TM. Influência do treinamento da musculatura respiratória e de membros inferiores no desempenho funcional de indivíduos com DPOC. Fisioter Pesq. 2010;17(3):209-13. doi:10.1590/S1413-81232010000500004.

17. Nygaard S, Christensen AH, Rold K, Nytrøen K, Guillemard L, Fiane A, et al. Autonomic cardiovascular control changes in recent heart transplant recipients lead to physiological limitations in response to orthostatic challenge and isometric exercise. Eur J Appl Physiol. 2019;119(10):2225-36. doi:10.1007/s00427-019-04207-5.

18. Nelson RR, Gobel FL, Jorgensen CR, Wang K, Wang Y, Taylor HL. Hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. Circulation. 1974;50(6):179-89. doi:10.1161/01.cir.50.6.179.

19. Sadrzadeh Rafie AH, Sungar GW, Dewey FE, Hadley D, Myers J, Froelicher VF. Prognostic value of double product reserve. Eur J Cardiovasc Prev Rehabil. 2008;15(5):541-7. doi:10.1097/JHJ.0b013e3282b305deef.

20. Domka-Jopek E, Jopek A, Bejer A, Lenart-Domka E, Walawski G. The importance of the double product in the six-minute walk test to predict myocardial function. Biomed Res Int. 2018;2018:3082690. doi:10.1155/2018/3082690.

21. Sniecinski RM, Skubas NJ, London MJ. Testing cardiac reserve: then and now. 1923. Anesth Analg. 2012;115(5):991-2. doi:10.1213/ANE.0b013e3182b2d209.

22. Mietus JE, Peng CK, Henry I, Goldsmith RL, Goldenberger AL. The pNnx files: re-examining a widely used heart rate variability measure. Heart. 2002;88(4):378-80. doi:10.1136/heart.88.4.378.

23. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health. 2017;5:258. doi:10.3389/fpubh.2017.00258.

464

Brazilian Journal of Cardiovascular Surgery

Braz J Cardiovasc Surg 2022;37(4):454-465

Junior LFR, et al. - Autonomic Function and Quality of Life in Heart Transplant
24. Hathaway DK, Wicks MN, Cashion A, Milstead EJ, Cowan PA, Gaber AO. Posttransplant improvement in heart rate variability correlates with improved quality of life. West J Nurs Res. 1998;65(5). doi: 10.1177/01939450022044728.
25. Hasan W. Autonomic cardiac innervation: development and adult plasticity. Organogenesis. 2013;9(3):176-93. doi:10.4161/org.24892.
26. Gordon R, Gwathmey JK, Xie LH. Autonomic and endocrine control of cardiovascular function. World J Cardiol. 2015;7(4):204-14. doi:10.4330/wjc.v7.i4.204.
27. Arrowood JA, Minisi AJ, Goudreau E, Davis AB, King AL. Absence of parasympathetic control of heart rate after human orthotopic cardiac transplantation. Circulation. 1997;96(10):3492-8. doi:10.1161/01.cir.96.10.3492.
28. Sheng Y, Zhu L. The crosstalk between autonomic nervous system and blood vessels. Int J Physiol Pathophysiol Pharmacol. 2018;10(1):17-28.
29. Yoshitatsu M, Ohtake S, Sawa Y, Fukushima N, Nishimura M, Sakakida S, et al. Assessment of autonomic reinnervation of cardiac grafts by analysis of heart rate variability. Transplant Proc. 2000;32(7):2383-5. doi:10.1016/s0041-1345(00)01709-7.
30. Guimarães GV, D’Avila V, Bocchi EA, Carvalho VO. Norepinephrine remains increased in the six-minute walking test after heart transplantation. Clinics (Sao Paulo). 2010;65(6):587-91. doi:10.1590/S1807-59322010000600005.
31. Carroll I, Mackey S, Gaeta R. The role of adrenergic receptors and pain: the good, the bad, and the unknown. Semin Anesth. 2007;26(1):17-21. doi:10.1053/j.sane.2006.11.005.
32. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med. 1995;41(10):1403-9. doi:10.1016/0277-9536(95)00112-k.
33. Higginson IJ, Carr AJ. Measuring quality of life: using quality of life measures in the clinical setting. BMJ. 2001;322(7297):1297-300. doi:10.1136/bmj.322.7297.1297.
34. Sessa F, Anna V, Messina G, Cibelli G, Monda V, Marsala G, et al. Heart rate variability as predictive factor for sudden cardiac death. Aging (Albany NY). 2018;10(2):166-77. doi:10.18632/aging.101386.
35. Kubota Y, Chen LY, White  EA, Folsom AR. Heart rate variability and lifetime risk of cardiovascular disease: the atherosclerosis risk in communities study. Ann Epidemiol. 2017;27(10):619-25.e2. doi:10.1016/j.annepidem.2017.08.024.