

Preoperative vagal activity predicts clinical outcomes after total knee replacement

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Abstract. Total knee replacement (TKR) surgery carries with it significant surgical trauma and activates complex inflammatory pathways, which initially assist healing. However, impaired regulation of inflammatory pathways can cause tissue damage and postoperative complications. The vagus nerve regulates inflammation, the activity of which is indexed by heart-rate variability (HRV), which predicts postoperative pain, longer hospitalization and improved recovery during the postoperative period. The present study examined the relationship between presurgical HRV, inflammation and complications after TKR. The present study assessed data from 41 patients undergoing TKR. A retrospective design was used, where preoperative electrocardiograms were scanned to determine HRV. Outcome measures included inflammation [C-reactive protein (CRP) levels] over four postoperative days, length of stay (LOS), and complications. Preoperative HRV predicted the trajectory of postoperative CRP levels. The low HRV group demonstrated higher overall postoperative CRP and a longer time to recover than patients with high HRV. Furthermore, the magnitude of inflammatory decline between postoperative days two and four was associated with LOS. However, HRV did not predict postoperative complications. In conclusion, patients with lower presurgical vagal activity had a worse postoperative inflammatory profile than those with high vagal tone. In the age of personalized medicine, such findings may have implications for identifying and preparing patients before surgery.

Introduction

As a result of sufficient wear and tear of the knee joint, patients can suffer from advanced osteoarthritis, leading to significant pain and disability; therefore, total knee replacement (TKR) surgery may be considered. During this surgical procedure, the femoral and tibial components of the knee are resected and replaced with artificial metallic elements with a polyethylene liner between them. The most common indication for TKR is severe arthrosis causing pain, stiffness, instability and deformity, leading to disability and a poor quality of life. Arthrosis may be caused by arthritis or previous trauma (1). TKR can alleviate knee pain, improve joint function by increasing the range of motion and enhance the quality of life for patients (2-4). However, no surgical procedure is without risk, and the most common side effects after TKR include deep vein thrombosis, infection, stiffness and osteolysis (5).

Surgical trauma in response to TKR is vast and activates complex inflammatory pathways crucial to post-surgical healing (6). Short-term inflammatory processes, including the release of pro-inflammatory cytokines (IL-1, IL-8 and TNF), are essential for protecting against infections, and for tissue repair and remodeling (7). In a balanced physiological system, anti-inflammatory processes regulate the pro-inflammatory response, orchestrated by the anti-inflammatory pathway of the vagus nerve (8-12). However, a lack of short-term inflammatory response regulation can cause longer and stronger inflammatory responses, potentially causing local tissue damage, shock, multiple organ dysfunction syndromes and even death (13).

The vagus nerve is the main branch of the parasympathetic nervous system. Its activity is indexed by the change in regular cardiac interbeat intervals, termed heart-rate variability (HRV). HRV, derived from electrocardiograms (ECGs), is strongly correlated with actual vagal nerve activity ($r=0.88$) (14). HRV has clinical importance because cardiac vagal tone is a marker of disease and adaptability. Low HRV levels predict all-cause mortality (15), worse prognosis after myocardial infarctions (16), and worse cancer prognosis (17), as well as psychopathology, such as stress, anxiety and depression (18), which is essential for postoperative rehabilitation. For example, several studies have demonstrated a relationship between preoperative HRV and postoperative outcomes.

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Low HRV has been reported to be associated with prolonged hospitalization (19), worse pain control (20) and decreased improvements during the postoperative period (21). However, to the best of our knowledge, no study has tested the relationship between preoperative HRV and short-term outcomes following TKR.

In the present study, the relationships between preoperative vagal activity (HRV) and postoperative outcomes, including complications, infections, inflammation [indexed by C-reactive protein (CRP) levels] and postoperative length of stay (LOS), were examined in patients undergoing TKR.

Materials and methods

Participants. A retrospective study design was used in the present study. After obtaining approval (approval no. 0082-20-BNZ) from the Ethics Committee of Bnai-Zion Medical Center (Haifa, Israel), background and medical information were collected from 156 medical records of patients who underwent TKR surgery at the Department of Orthopedic Surgery (Bnai Zion Medical Center) between January 2018 and December 2020. The inclusion and exclusion criteria were as follows: To be included in the study, participants were required to be aged >18 years, have a clear preoperative ECG, and possess recorded CRP measurements on days 1, 2 and 4 after surgery. Additionally, there was a need for thorough documentation of their postoperative follow-up. Patients were not excluded based on any comorbidities. Of the 156 files, 38 had no ECG data in their files, and 77 of the remaining excluded files had unreadable paper ECG data. Finally, all data used for the present study were collected from 41 patients.

Background information. The background information collected included patient age, sex, comorbidities (hypertension, diabetes, cancer, heart diseases and dyslipidemia), and operation side. TKR surgery was not conducted on patients with existing infections; therefore, no study participants had preoperative infections.

Vagal nerve tone was indexed according to HRV. HRV was derived from preoperative 10-sec segments of the patients' ECGs. This included the time-domain HRV markers of standard deviation of normal-to-normal RR-intervals (SDNN) and root mean square of successive differences (RMSSD). HRV, as measured by ultra-short 10-sec ECGs, has been demonstrated to predict heart failure (22), all-cause mortality (23) and cancer survival (24,25). Scanning the ECGs into a digital file, SDNN and RMSSD were mathematically derived with a specific code developed using MATLAB software (version R2020a; <https://www.mathworks.com/help/releases/R2020a.html>). The MATLAB algorithm collects two vectors of data, one representing the time in milliseconds and the other the amplitude in millivolts in the waveforms. From these vectors, the variance of the RR intervals was measured, from which SDNN and RMSSD were derived using standard formulas (26,27).

Clinical outcomes. Outcomes were obtained from the patient's electronic medical files. These included the levels of CRP on postoperative days 1, 2 and 4, as well as LOS in the hospital. Finally, information was also obtained about any postoperative infections.

Statistical analysis. SPSS version 26 (IBM Corp.) was utilized for a comprehensive statistical analysis. Initially, descriptive statistics, such as percentages, mean and median values, and standard deviation (SD) values were calculated for all main variables, with the aim of understanding the fundamental trends of the data. Subsequently, inferential statistics were employed, focusing on the relationships between HRV levels, CRP and LOS in the postoperative phase, using the Pearson correlation coefficient.

A critical component of the present study was the mixed-design analysis of variance (ANOVA), which examined the effects of HRV categories (high or low; patients were divided into high and low HRV groups by designating them as above or below 15 msec for SDNN or 20 msec for RMSSD, reflecting the sample medians of each parameter) and time (postoperative days 1, 2 and 4) on CRP levels. This method was pivotal in determining how HRV influences the postoperative CRP trajectory. The post hoc analyses included t-tests on changes in CRP levels between high and low HRV groups. Sidak's significance level was then calculated, assuming the use of two post hoc tests due to performing multiple comparisons. This yielded a critical P-value of 0.025.

Results

Patient demographics and baseline characteristics. Of the 41 patients, 41.5% were men, and 58.5% were women. Patient ages ranged from 43 to 84 years, with a mean \pm SD of 68.6 ± 10.1 years. Comorbidities included hypertension (65.9%), hyperlipidemia (41.5%), diabetes (31.7%), heart disease (29.3%) and cancer (7.3%). A higher percentage of right-sided TKR surgeries was performed (63.4%) compared with left-sided surgeries (36.6%). The rate of complications was 12%, including deep vein thrombosis (2.4%), cellulitis (4.8%), acute myocardial infarction (2.4%) and cerebrovascular accident (2.4%). Notably, the cohort did not include any patients with rheumatic diseases. The descriptive statistics of the two HRV parameters obtained from patient ECGs are presented in Table I.

HRV analysis. The patients were then divided into high and low HRV groups by designating them as above or below 15 msec for SDNN or 20 msec for RMSSD, reflecting the sample medians of each parameter.

Postoperative clinical outcomes. LOS ranged from 2 to 22 days, with a mean \pm SD of 6.22 ± 3.44 days, as shown in Table II, along with CRP levels on postoperative days 1 (49.00, SD=26.25), 2 (164.19, SD=85.55) and 4 (146.76, SD=48.98). Notably, Table I shows that the standard deviation of HRV exceeded the mean value, suggesting that the data do not follow a normal distribution and thus cannot be accurately described by the mean \pm SD format. Consequently, a logarithmic transformation was applied to HRV to normalize its distribution. Furthermore, the primary analysis focused on categorical HRV (high/low), rendering the issue of normality moot.

Statistical analyses and findings. Using a mixed design-ANOVA, a significant effect of time on CRP levels was determined ($P < 0.001$) and a trend toward a significant

Table I. Heart-rate variability 10-sec time domain parameters from patients' electrocardiograms.

Variable	Median, msec	Mean, msec	Standard deviation, msec
SDNN	15	28.08	33.69
RMSSD	20	39.56	47.09

SDNN, standard deviation of normal-to-normal RR-intervals; RMSSD, root mean square of successive differences.

Table II. Mean and standard deviation of LOS and CRP levels on postoperative days 1, 2 and 4.

Variable	Mean	Standard deviation
LOS, days	6.22	3.44
CRP, mg/l		
Day 1	49.00	26.25
Day 2	164.19	85.55
Day 4	146.76	48.98

CRP, C-reactive protein; LOS, length of stay.

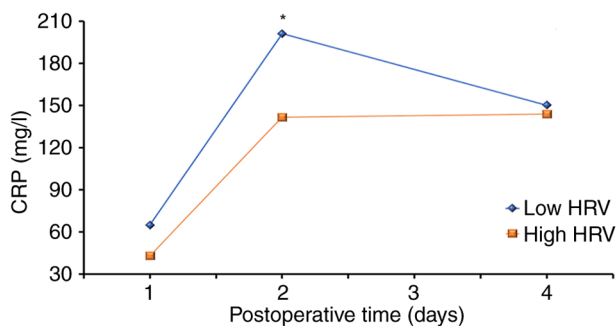


Figure 1. CRP levels on postoperative days 1, 2 and 4, for patients with low and high HRV. * $P < 0.05$ vs. the high HRV group. CRP, C-reactive protein; HRV, heart-rate variability.

HRV x time interaction ($P < 0.058$) in relation to CRP was revealed (Fig. 1). This revealed differences in the CRP levels during postoperative days as a function of patients' baseline HRV. The low HRV group demonstrated higher overall CRP levels on all postoperative days. It took patients with low HRV more time to recover, as seen by the trajectory of the inflammatory marker CRP, compared with patients with high HRV (Fig. 1; Table III). The effect of time on CRP was significant ($P < 0.001$), whereas HRV alone did not have a significant effect on CRP ($P = 0.15$). When trying to identify the source of the HRV x time interaction, a t-test was used to compare between subjects. The change in CRP from day 2 to day 4 after surgery, in patients with low HRV was significantly larger (47.64) than that in patients with high HRV [2.24; $t(23) = 2.44$, $P = 0.023$]. This revealed that the trajectory of postoperative CRP differed according to patients' baseline HRV levels.

Table III. CRP levels on postoperative days 1, 2 and 4, as a function of patients' baseline HRV.

Variable	Vagal tone	Mean, mg/l	Standard deviation, mg/l
CRP day 1	Low HRV	64.78	27.98
	High HRV	43.10	24.77
CRP day 2	Low HRV	201.08	87.79
	High HRV	141.56	68.58
CRP day 4	Low HRV	150.25	45.16
	High HRV	143.80	54.36

CRP, C-reactive protein; HRV, heart-rate variability.

Upon initial analysis, none of the confounding variables (such as age and background illnesses), except sex ($P > 0.05$), were significantly related to HRV ($P > 0.05$; Table SI). In addition, no significant correlation was identified between HRV and LOS (for SDNN: $r = 0.13$, $P = 0.41$; for RMSSD: $r = 0.10$, $P = 0.52$) (data not shown). The changes in CRP on days 2 and 4 (CRP4-CRP2) were calculated. When examining the relationship between LOS and change in CRP levels between postoperative days 2 and 4 (in which HRV groups differed), a significant correlation was identified between Δ -CRP on days 2 and 4 with LOS ($r = -0.61$, $P = 0.034$), only in patients with low HRV. These findings indicated that the greater the decrease in inflammation between days 2 and 4, the shorter the LOS in the low HRV group. By contrast, no similar correlation was detected among patients in the high HRV group, referring to Δ -CRP on days 2 and 4 with LOS ($r = -0.36$, $P = 0.23$). When analyzing the results for confounding variables, it was demonstrated that only pre-existing heart disease was positively correlated with the patients' LOS (Table SI). After statistically controlling the effects of heart disease (using a partial correlation analysis) the correlation between LOS and change in CRP between days 2 and 4 was no longer significant (but still strong and negative; $r = -0.46$, $P = 0.12$) in patients with low HRV. Moreover, none of the patients' background variables (age, sex or other comorbid diseases) were related to the inflammatory trajectory according to the CRP levels (Table SI).

Finally, no significant association was detected between HRV and complication rate using t tests (for SDNN, $P > 0.05$; for RMSSD, $P > 0.05$). Partial η^2 for the ANOVA on CRP levels (time effect) was reported as ~ 0.749 ; this value indicates a large effect size, based on the conventional benchmarks where η^2 values of 0.01, 0.06 and 0.14 represent small, medium and large effects, respectively. Cohen's d for the t-test between CRP changes in the high and low HRV groups was reported as ~ 1.021 . This value also indicates a large effect size based on conventional benchmarks where Cohen's d values of 0.2, 0.5 and 0.8 represent small, medium and large effects, respectively.

Discussion

The present study examined the postoperative inflammatory response after TKR surgery as a function of patients' preoperative vagal tone, indexed by HRV. The results demonstrated

that patients took a longer time to resume baseline levels of postoperative HRV if their preoperative HRV levels were low. Moreover, a significant correlation was revealed between inflammatory change across recovery days and LOS. Patients with lower vagal tone demonstrated a longer inflammatory recovery time, with a more significant decrease in CRP between postoperative days 2 and 4, when compared to patients with higher vagal tone. Moreover, in the low HRV group only, the magnitude of CRP decline between postoperative days 2 and 4 was correlated with their LOS, revealing the clinical significance of the CRP trajectory. The level of CRP before surgery may also be an important factor, but it was not analyzed because the present study focused on routinely measured data only, and no patients in the present cohort had undergone preoperative CRP measurements.

To gather the two time-domain measurements of HRV: SDNN and RMSSD, preoperative ECGs were used, since ECG tests are mandatory before TKR surgery. Reduced HRV is known to be associated with several chronic diseases and poor outcomes, such as hypertension (28,29), systematic inflammation (30,31), diabetes (32), and increasing age. Studies have shown abundant evidence for the significant prognostic value of HRV in conditions such as myocardial infarction (16) and cancer (17,24). However, this broad spectrum of associated diseases and influencing factors suggests that low HRV may have low specificity in the distinction between specific illnesses. The mean values of HRV observed in the present cohort were in line with the normal range of HRVs concerning the influence of age and medical history. The median of RMSSD and SDNN (20 and 15 msec, respectively) corresponded to low levels in the normal range of HRVs referenced in the literature (33,34), that are mainly collected from cohorts with no significant medical conditions, which could affect HRV. By contrast, the present cohort exhibited several comorbidities, including hypertension, diabetes, heart disease and cancer. Therefore, given the known information and the medical history of the patients, the median HRVs observed in the present study appeared similar to the low cut-off of the normal range of HRVs, but well within the normative data concerning ultra-short measurements of 10-sec ECGs (33,34).

CRP is an acute-phase protein used as a marker of inflammation or infection in orthopedic surgery, including TKR. After infectious or inflammatory stimuli, serum CRP levels may rise abruptly, reaching up to 1,000 times the baseline value in 48 h (35). It has received particular attention due to its predictive role in several diseases and its relation to HRV indices (34,36). Several studies have examined the relationship between HRV and CRP across age groups (31,37-39), and have revealed that inflammatory parameters are strongly associated with decreased HRV. Moreover, a unique prospective study supporting the cholinergic anti-inflammatory role of the vagal nerve has been performed (40), which demonstrated that HRV levels at baseline can predict CRP levels 4 years later. CRP also has a vital role in orthopedics, and can be used in the diagnosis and follow-up of infections (41).

The vagus nerve regulates peripheral inflammation via two mechanisms. First, after peripheral monocytes secrete IL-1, that signal binds to IL-1 receptors on the vagal paraganglia. This is then translated to a cholinergic signal and reaches the hypothalamus, where it activates the

hypothalamic-pituitary-adrenal axis, resulting in cortisol secretion, which reduces inflammation. Second, the efferent vagus converts at the celiac ganglion to a sympathetic branch, which enters the spleen. There, a sub-type of residing T cells express the β -adrenergic receptor, which upon stimulation secretes acetylcholine. That neurotransmitter then binds to the α -7 nicotinic acetylcholine receptor on residing macrophages, and this inhibits their production of pro-inflammatory cytokines (8-12).

The results of the present study demonstrated that the behavior of the inflammatory index CRP among the patients assessed, exhibited similarities to the existing data in the literature among patients following TKR. Several studies have demonstrated a specific pattern for CRP change following TKR and have shown that CRP levels typically peak within 48 h following surgery and decrease significantly by postoperative day 4 (42-44). It has also been reported that rising CRP levels after postoperative day 3 may indicate a complication of surgery, such as infection. The rise in CRP following surgical trauma is used post-operatively to quantify the degree of tissue damage and deduce the operative stress experienced by the patient. The present results demonstrated the known increases and decreases in CRP over 4 postoperative days (42-44).

Moreover, when examining the CRP dynamics as a function of patients' baseline HRV, two distinct profiles of CRP dynamics emerged. Patients with low vagal tone exhibited a higher inflammatory peak, which was associated with a more extended inflammatory recovery period than patients with high vagal tone. This finding expands existing knowledge about the relationship between the autonomic nervous system and inflammatory processes after surgical trauma. These results could also help orthopedic surgeons know in advance which patients may display postoperative inflammatory complications.

A limitation of the present study is the relatively small number of patients included in the final analysis, which arises from the retrospective nature of the study in which preoperative paper ECGs were collected. Often, these ECGs were degraded to the point where HRV could not be reliably analyzed. Therefore, only ECGs that were readable and allowed for accurate HRV analysis were used, and no degraded files were used. Another important issue is that the present study did not gather information on the intake of medications, such as β -blockers, although they are known to influence vagal tone (41). Another problem is that each preoperative ECG came from a different clinic, and hence they were not standardized. Nevertheless, the finding that baseline HRV does predict the postoperative trajectory of CRP shows the robustness of this relationship. In future studies, these results need to be replicated by implementing a prospective study design using a single ECG machine to generate digital ECGs. Conducting a prospective study will also allow for further data collection via patient self-report questionnaires (e.g., to assess stress levels), long-term follow-up and vagal tone interventions (45) that may lead to better patient-specific preoperative preparation.

Personalized medicine with the goal of 'the right treatment to the right patient at the right time' (46) is defined as the prevention of chronic diseases, early intervention and personalized treatment planning (47). Patient HRV is known to be affected by numerous parameters, such as sex and age (48,49),

circadian rhythms (50,51), mental and physical activity, and ethnicity (52-54). Hence, knowledge of patients' HRV should allow for better patient-specific preoperative and postoperative treatment plans resulting in improved recovery, fewer complications and greater patient satisfaction.

Knowledge of patient preoperative vagal tone allows for behavioral and biofeedback interventions as part of surgical preparation. Recognizing the presurgical stress and psychopathology of patients via their HRV (18), can enable clinicians to provide them with important information and valuable coping skills. Psychological screening and evaluation could address stress and anxiety before the surgical procedure. It also assists in altering risky personal habits that adversely affect vagal tone and surgery outcomes, such as smoking cessation, developing adapted eating habits, promoting physical activity and acknowledging the candidate's concerns regarding the expected surgical results.

However, surgical recovery may also be possibly influenced by activating the vagus via biofeedback. Biofeedback is based on the collection and visualization of biological activities and teaching patients to modify a certain biological parameter. This can empower users to control their physiological processes in conjunction with changes to their psychological state. Biofeedback has demonstrated effectiveness in managing different diseases by increasing vagal activity and improving the autonomic nervous system balance. Specifically, HRV biofeedback (HRVB) involves the modulation of the autonomic nervous system through slow-paced breathing. HRVB is considered a learned skill that maximizes HRV, and facilitates autonomic and cardio-respiratory homeostasis (55). Typically, HRVB is guided by a visual and auditory representation of one's heartbeat or HRV in real-time to support the process of increasing the amplitude of HRV (56). Several systemic reviews have examined the effects of biofeedback on stress and anxiety, depression, emotional and physical health, and the applicability of the HRVB intervention among populations of patients with chronic diseases (57-61). These reviews show that HRVB training is associated with a considerable reduction in self-reported stress and anxiety, improves depressive symptoms, improves behavioral symptoms (such as arousal) and functioning (such as avoidance) and various patient clinical outcomes, including hypertension and cardiovascular prognosis, inflammatory states and pain.

In conclusion, the present study highlighted the significant impact of presurgical vagal activity on postoperative inflammatory response following TKR surgery. Patients with lower vagal activity experienced worse outcomes, while the magnitude of inflammatory decline was correlated with hospital stay. This knowledge may improve presurgical interventions to enhance surgical outcomes and patient well-being. Future research should explore behavioral and biofeedback interventions to enhance presurgical vagal tone, potentially reducing stress, improving recovery and increasing patient satisfaction. These findings hold great promise for personalized medicine and transformative advancements in surgical practice.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AG and ADL were involved in study conception and design, data collection, analysis and interpretation of the results, and manuscript writing. AEAA and AGM were involved in data collection. OBL was involved in study conception and design, and performed clinical supervision. YG was involved in study conception and design, and analysis and interpretation of results. AG and ADL confirm the authenticity of all the raw data. All authors reviewed the results, and read and approved the final manuscript.

Ethics approval and consent to participate

The research was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Bnai-Zion Medical Center (approval no. 0082-20-BNZ).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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