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Autonomic regulation of systemic inflammation in humans: a multi-center, blinded observational cohort study.

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Abstract

Objective: Experimental animal models demonstrate that autonomic activity regulates systemic inflammation. By contrast, human studies are limited in number and exclusively use heart rate variability (HRV) as an index of cardiac autonomic regulation. HRV measures are primarily dependent on, and need to be corrected for, heart rate. Thus, independent autonomic measures are required to confirm HRV-based findings. Here, the authors sought to replicate the findings of preceding HRV-based studies by using HRV-independent, exercise-evoked sympathetic and parasympathetic measures of cardiac autonomic regulation to examine the relationship between autonomic function and systemic inflammation.

Methods: Sympathetic function was assessed by measuring heart rate changes during unloaded pedaling prior to onset of exercise, divided into quartiles; an anticipatory heart rate (AHRR) rise during this period is evoked by mental stress in many individuals. Parasympathetic function was assessed by heart rate recovery (HRR) 60s after finishing cardiopulmonary exercise testing, divided into quartiles. Parasympathetic dysfunction was defined by delayed heart rate recovery (HRR) $\leq$12.beats.min^{-1}, a threshold value associated with higher cardiovascular morbidity/ mortality in the general population. Systemic inflammation was primarily assessed by neutrophil-lymphocyte ratio (NLR), where a ratio >4 is prognostic across several inflammatory diseases and correlates strongly with elevated plasma levels of pro-inflammatory cytokines. High-sensitivity C-reactive protein (hsCRP) was also measured.

Results: In 1624 subjects (65$\pm$14y; 67.9% male), lower HRR (impaired vagal activity) was associated with progressively higher NLR (p=0.004 for trend across quartiles). Delayed HRR, recorded in 646/1624 (39.6%) subjects, was associated with neutrophil-lymphocyte ratio>4 (relative risk:1.43 (95%CI:1.18-1.74); *P*=0.0003). Similar results were found for

hsCRP (p=0.045). By contrast, AHRR was not associated with NLR (relative risk:1.43 (95%CI:1.18-1.74); p=0.48).

Conclusions: Delayed HRR, a robust measure of parasympathetic dysfunction, is independently associated with leukocyte ratios indicative of systemic inflammation. These results further support a role for parasympathetic modulation of systemic inflammation in humans.

Keywords: Autonomic; inflammation; parasympathetic; sympathetic; exercise

1. Introduction

Experimental models show that neural mechanisms play a fundamental role in regulating systemic inflammation. The preservation, or augmentation, of efferent parasympathetic activity via the vagus nerve reduces systemic inflammation (Andersson and Tracey, 2012a), including in patients with rheumatoid arthritis. (Koopman et al., 2016a) Cholinergic activation of the α7 subunit of the nicotinic acetylcholine receptor in macrophages reduces TNF release (Bernik et al., 2002) and impairs migration of leukocytes to inflammatory sites. (Saeed et al., 2005) The sympathetic nervous system also regulates inflammation through modulation of macrophage and lymphocyte function as well as leukocyte trafficking. (Elenkov et al., 2000) Apparently healthy subjects with impaired autonomic function may therefore be at particular risk of sustaining infectious complications (Ackland et al., 2016a; Toner et al., 2016) and autoimmune disease. (Koopman et al., 2016b)

Beyond experimental laboratory models, a particular challenge in humans is assessing the role of vagally-mediated and sympathetically-mediated effects on inflammation. All studies to date have linked inflammation and autonomic function through the measurement of heart rate variability (HRV). However, commonly used time- and frequency-domain measures of HRV are non-linearly dependent on heart rate, bringing into question the basis of HRV as a robust measure of autonomic function. (Monfredi et al., 2014) Thus low HRV is intrinsically linked to a higher HR, bringing into question whether relative bradycardia occurs as a result of high vagal tone rather than remodelling of the sinoatrial node. These data suggest additional, heart rate and HRV-independent measures of autonomic function would provide further evidence for autonomic modulation of inflammation in humans, and potentially delineate a novel biomarker to identify subjects who may benefit from neuromodulatory interventions.

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Cardiopulmonary exercise testing provides a standardized dynamic challenge for sympathetic and parasympathetic limbs of the autonomic nervous system. Sympathetic activation is frequently elicited in many individuals through the mental stress evoked during unloaded pedaling prior to ramped exercise (Jouven et al., 2009)- a feature the authors have termed anticipatory heart rate rise. (Whittle et al., 2015) At the end of exercise, vagal reactivation initiates the deceleration of heart rate (termed heart rate recovery (Coote, 2010)), as demonstrated by its blockade by atropine. (Imai et al., 1994)(Fisher et al., 2006; Savin et al., 1982) Low heart rate recovery in apparently otherwise healthy individuals is independently associated with excess mortality. (Cole et al., 1999; Vivekananthan et al., 2003)

Here, we undertook a prospective observational cohort study designed to re-examine the findings of preceding HRV-based studies, by establishing the relationship between HRV-independent, exercise-evoked sympathetic and parasympathetic measures of cardiac autonomic regulation and systemic inflammation. Neutrophil-to-lymphocyte ratio was used as an established, routinely obtained biomarker for subclinical inflammation that correlates strongly with elevated plasma levels of circulating pro-inflammatory cytokines (Chen et al., 2015; Kantola et al., 2012) and adverse clinical outcomes, as shown from studies totaling 47000 subjects. (Templeton et al., 2014)(Shah et al., 2014)

2. **Methods**

2.1   Participants

This prospective observational study was approved by the NRES Committee London (Camden & Islington; MREC: 12/LO/0453). Subjects gave written, informed consent prior to undergoing cardiopulmonary exercise testing. Inclusion criteria were any patient

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scheduled for major surgery referred to their local cardiopulmonary exercise testing service as part of their routine preoperative assessment. Exclusion criteria included refusal of consent or contraindication to undertake cardiopulmonary exercise testing. Patient age, gender, body-mass index, drug therapy and cardiometabolic comorbidities, including diabetes mellitus and hemoglobin were recorded.

2.2 Cardiopulmonary exercise testing.

Patients undertook cardiopulmonary exercise testing on an electronic cycle ergometer to maximal tolerance, having continued their normal cardiovascular medications up to and including the day of the test. None were limited by active pain. Participants sat quietly on the CPET bike, and were not engaged in any other activity. Baseline heart rate was recorded while the patient sat at rest for 3 minutes, after which unloaded pedalling was undertaken for a fixed period (3 minutes) prior to the ramped exercise protocol commencing. (Whittle et al, 2015) Only CPET technicians were present in the room only; conversations were restricted to explaining the process of the CPET test with participants.

Continuous 12-lead electrocardiogram was recorded. Equipment was calibrated before each test using standard reference gases. Continuous breath-by-breath gas exchange analysis was performed. All patients were instructed to continue cycling until symptom-limited fatigue occurred. Anaerobic threshold (AT) was determined by two independent assessors blinded to heart rate recovery and according to published guidelines using the modified V-slope method and confirmed by ventilatory equivalents for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) and oxygen ($\dot{V}_E/\dot{V}O_2$). (Beaver et al., 1986) Personnel who carried out all exercise testing and patients were blinded to anticipatory heart rate increase and heart rate recovery data as these were not provided in reports to clinical teams.

2.3   Sympathetic and parasympathetic measures.

Anticipatory heart rate rise (AHRR) was defined as an increase in heart rate ≥12 beats.min^{-1} during unloaded pedaling undertaken for a fixed period (3 minutes) prior to the ramped exercise protocol commencing. (Whittle et al, 2015 (Jouven et al., 2009)) Heart rate increase (HRI) was calculated from the difference between peak and baseline heart rate (Figure 1). Heart rate recovery (HRR) was recorded 1 minute after the end of peak exercise, when subjects remained in the seated position (Figure 1). Subjects were prospectively classified as having normal or delayed heart rate recovery (HRR) based on (seated) at 1 minute ≤12 beats.min^{-1} A mechanistic study in perioperative patients (Ackland et al., 2016b) and treadmill exercise studies reported that this threshold is independently with excess mortality. (Cole et al., 1999; Vivekananthan et al., 2003). We have previously shown that HRR correlates strongly with the high frequency component of the HRV power spectrum (Ackland et al., 2016b), an accepted and widely used HRV measure of parasympathetic activity (see Supplemental Figure 1 for relationship between HF-HRV and HRV obtained from patients separate to the current study, as detailed in Ackland et al., 2016b).

2.4 Inflammatory markers

Blood samples were obtained on a separate day to the cardiopulmonary exercise test, by individuals masked to the CPET data. Blood samples were collected before exercise testing, typically a week beforehand. Preoperative leukocyte subsets were measured using a Sysmex XE2100 analyzer (Sysmex, Milton Keynes, UK). A priori, neutrophil-to-lymphocyte ratio >4 was used as an established median threshold value associated with subclinical inflammation and adverse clinical outcomes derived from studies totaling 40559 patients. (Templeton et al., 2014) Lymphopenia (lymphocyte count <20% total leukocytes) was also assessed as an additional marker of chronic inflammation, characterized by mitochondrial dysfunction and

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impaired T cell function. (Edwards et al., 2015) In a subset of subjects, plasma high-sensitivity C-reactive protein (hsCRP) levels, a negative prognostic inflammatory biomarker for the development of cardiometabolic disease, was also assessed (Kaptoge et al., 2010) Since hsCRP levels >3 mg/L are strongly associated with relative excess risk of cardiovascular disease, in the context of other traditional risk factors, (Kaptoge et al., 2010) data were analyzed on the basis of this hsCRP threshold value.

2.5 Statistical analysis

Categorical data are summarized as absolute values (percentage). Continuous data are presented as mean (95% confidence intervals). AHRR and HRR were binned by quartile to assess whether a "dose-response" relationship existed between each measure and markers of systemic inflammation. Manual and automated validation checks of data were performed both centrally and through source data verification. The primary explanatory outcome was the relative risk of patients with HRR≤12 having prognostically significant preoperative levels of systemic inflammation, as reflected by neutrophil-to-lymphocyte ratio >4. Characteristics of subjects with/ without HRR ≤12 beats.min^{-1} or AHRR≥12 beats.min^{-1} were compared using the Fishers exact test for trend. Continuous data were analyzed using ANCOVA (controlling for age, gender, body-mass index), with post-hoc Tukey Kramer tests to identify within and between factor differences. Regression analysis applied in other fields was undertaken (Rezaei et al., 2016; Valipour, 2016; Valipour et al., 2013), using a one-way, hierarchical forward switching model (Hintze, 2015) to establish the relationship between covariates (age, gender, body-mass index, diabetes mellitus, cardiovascular disease), drug therapy known to affect autonomic function (statins, beta blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel antagonists) and baseline heart rate, anticipatory heart rate and heart rate recovery. To assess

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whether a linear relationship may exist between NLR and HRR/AHRR as continuous variables, the Passing-Bablok linear regression model was used. P<0.05 was considered significant. All statistical analyses were undertaken using NCSS 11 (Kaysville, UT, USA). Sample size was calculated to detect differences in proportion of patients with NLR>4, assuming a population incidence of ~20%. From our previous work, subjects with delayed heart recovery were predicted to comprise ~ 30% of this population. To detect a critical difference between proportions in NLR>4 of at least 10%, >1508 subjects in total would be required (α=0.01; β=0.9).

3. Results

3.1 Subject characteristics.

Recruited subjects had a mean age 65±14 years, with male gender representing ~67% (Table 1). Diabetes mellitus was present in ~7% subjects; 46% received cardiovascular medication but chiefly for essential hypertension. Inflammatory disease (including rheumatoid arthritis, vasculitidies and inflammatory bowel disease requiring immunosuppressive drug treatment) comprised less than 14% of the total population. Clinically treated depression/anxiety was present in 9.8% of the total population.

3.2 Sympathetic autonomic function and systemic inflammation

Autonomic measures made during exercise are summarized in Table 1. Anticipatory heart rate increases during unloaded pedalling were variable, with heart rate increases of >10% from baseline occurring in 55% of subjects pedalling during the exercise warmup period. Analysis by quartile of anticipatory heart rate rise (AHRR) did not show any association with NLR ($F_{(3,1514)}$ =0.84; *P*=0.47; Figure 1A, B; Supplementary Figure 2). Similarly, using a previously defined threshold value for AHRR associated with sympathetic-induced changes

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in cardiac ischemia during exercise, (Whittle et al., 2015) no association with NLR was found (relative risk:1.24 (95%CI:0.94-1.65); *P*=0.14).

3.3 Parasympathetic autonomic function and systemic inflammation

Progressively lower HRR (Figure 1C, D) was associated with a graded increase in neutrophil-lymphocyte ratio, controlling for age, gender and body-mass index ($F_{(3,1511)}$=3.4; *P*=0.01); Figure 2E; Supplementary Figure 3). 600/1512 subjects had delayed HRR≤12, which was associated with neutrophil-lymphocyte ratio threshold value>4 (relative risk:1.41 (95%CI:1.17-1.71); *P*=0.0005). Multivariable logistic regression analysis showed that lower HRR was associated with higher NLR (Supplementary Table 1), taking into account aerobic fitness (anaerobic threshold), cardiovascular medications, diabetes and age. Similarly, higher total leukocyte count showed a significant graded relationship with heart rate recovery (Figure 1F). A lymphocyte fraction <20%, which is characterized by mitochondrial dysfunction and impaired T cell function, (Edwards et al., 2015) was also associated with delayed HRR≤12 (relative risk: 1.25 (95%CI: 1.08-1.46); p=0.004; Supplementary Figure 3).

3.4 Co-existence of sympathetic and parasympathetic impairment and systemic inflammation.

The presence of both parasympathetic (delayed HRR≤12) and sympathetic (AHRR≥12) impairment had similar higher NLR, compared to delayed HRR alone (p=0.65).

3.5 Parasympathetic impairment and high-sensitivity C-reactive protein.

In a subset of 177 subjects, 50/68 with delayed HRR≤12 had plasma high-sensitivity CRP >3mg.dl^{-1}, a negative prognostic factor for the development of cardiovascular disease, compared with 65/109 with higher HRR (relative risk: 1.23 (95%CI:1.00-1.52); P=0.04)).

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4.   Discussion

This multi-center, prospective, blinded, observational cohort study shows that impaired parasympathetic function, as reflected by heart rate recovery, is strongly associated with leukocyte subset measures indicative of systemic inflammation. We do not infer that HRR serves as a substitute measure for other established parasympathetic measures (e.g. HF-HRV) or that it is more instructive (given the lack of direct comparison with HRV measures), but rather adds further support to the hypothesis that parasympathetic autonomic neural activity regulates systemic inflammation. Subjects with delayed HRR were more likely to have markers of inflammation indicative of dysregulated immune function (neutrophil-to-lymphocyte and lymphocyte-to-monocyte ratios), ratios that several studies have independently found are associated with poorer clinical outcomes. (Edwards et al., 2015; Graziosi et al., 2015; Ji et al., 2016; Malietzis et al., 2014) These leukocyte subsets have consistently been shown to be useful prognostic biomarkers for both cardiovascular and perioperative morbidity, as well as cancer recurrence. However, the underlying reason for this association with elevated NLR has thus far remained unclear. Our data suggests that loss of parasympathetic autonomic activity contributes to this inflammatory phenotype.

Experimental and clinical translational studies suggest that the loss of parasympathetic efferent activity promotes cardiovascular impairment (Ackland et al., 2016b) and renal dysfunction, (Yeboah et al., 2008) in part through the promotion of systemic inflammation. Vagal neuromodulation limits tissue injury in a range of pathological settings. (Andersson and Tracey, 2012b; Cheyuo et al., 2011; dos Santos et al., 2011; Kox et al., 2011) Further reductions in parasympathetic activity following acute inflammatory insults (e.g. major surgery) may also contribute to postoperative morbidity. (Karmali et al., 2015) These findings mirror the established pathological role of autonomic dysfunction in cardiac failure,

where failure to improve autonomic function despite optimal medical therapy is associated with higher mortality. (Nolan et al., 1998)

Our data suggests that parasympathetic dysfunction provides a unifying, underlying mechanism linking various drivers of autonomic perturbation to higher levels of systemic inflammation. HRR was not affected by other chronic cardiovascular medication including β-blockade, as reported previously. (Karnik et al., 2008) Several large prospective studies have established varying thresholds for heart rate recovery following exercise that are associated with increased risk of mortality. Analysis of heart rate recovery after exercise across studies suggests that HRR values consistently identify patients at the highest risk of mortality regardless of which specific timepoint(s) are used. However, studies have employed variable exercise and recovery protocols, which impacts on the comparability of the absolute change in HRR. HRR was measured in the seated position following symptom limited maximal exercise, which offers a reproducible endpoint for comparison between subjects. The most stringent and widely adopted threshold of HRR≤12 described thus far was used, (Adabag and Pierpont, 2013) which from mechanistic work has related the low HRR phenotype to pathophysiology after major surgery and markedly lower vagal tone as measured by heart rate variability (Ackland et al., 2016b) As autonomic function improves with programmed exercise, (Fu and Levine, 2013) this approach may potentially reduce preoperative systemic inflammation.

High NLR values are associated with elevated cytokine markers of the systemic inflammatory response, including IL-1 receptor antagonist, IL-6, IL-8, IL-12, interferon γ, monocyte chemotactic protein 1, macrophage inflammatory protein 1β, and platelet-derived growth factor. (Kantola et al., 2012)(Chen et al., 2015) The choice of neutrophil-lymphocyte ratio as an inexpensive, readily available biomarker for systemic inflammation is reinforced by its predictive role established from a wealth of clinical epidemiologic data across diverse

pathologies that are underpinned by an inflammatory etiology. (Akpek et al., 2012; Nunez et al., 2008; Shah et al., 2014; Tamhane et al., 2008; Templeton et al., 2014; Uthamalingam et al., 2011)

Preceding studies that found high-sensitivity C-reactive protein (and/or its cytokine driver) to be inversely associated with time and frequency domain measures indicative of parasympathetic impairment in otherwise healthy individuals (Aeschbacher et al., 2017; Cooper et al., 2015; von Kanel et al., 2008; (Singh et al., 2009)) A similar relationship between hsCRP and HRR was observed for the first time, demonstrating that systemic inflammation is associated with this measure of parasympathetic function that is independent of HRV. Lower HRR associated with elevated levels of hsCRP>3mg.dl^{-1} that are associated with excess vascular risk (Ridker, 2016). Taken together, these data indicate a specific link between hsCRP and parasympathetic dysfunction. Our findings are therefore in keeping with several preceding studies using heart rate variability as a measure of autonomic imbalance in individuals at risk of disease progression, where a significant relationship between increased serum hsCRP and HRV was reported. (Anan et al., 2005; Frasure-Smith et al., 2009; Gunterberg et al., 2016; Kon et al., 2006; Lockwood et al., 2017) However, the hsCRP finding reported in this manuscript should be tempered by the findings of both NHANES (National Health and Nutrition Examination Survey) and MESA (Multi-Ethnic Study of Atherosclerosis) studies, which showed significant short-term intra-individual variability in plasma hsCRP levels. (Bower et al., 2012; DeGoma et al., 2012)

The chief novelty of this study is the use of HRV-independent measures of autonomic function evoked by exercise, plus the generalizable, large scale interrogation of systemic inflammation in parallel with two separate, but concomitant, measures of sympathetic and parasympathetic function. We acknowledge that HRR serves as an index of phasic, rather

than tonic, HRV and reflects the neurovisceral integration of autonomic, emotional, and cognitive factors that shape cardiac autonomic activity during voluntary exercise. (Thayer et al., 2009) Specific strengths of this prospective multi-center study are that primary study outcomes were blinded to delayed heart rate status. Subject demographics suggest that our findings are generalizable, occurring in an older population when autonomic impairment becomes increasingly prevalent. Having identified this phenotype, future work may reveal further mechanistic insights by more detailed interrogation of immune function using flow cytometry. Weaknesses of the study center on its' observational design, since causality cannot be inferred with this approach. While our previous study confirmed a strong correlation between HF-HRV and HRR (Ackland et al, 2016), the data reported herein would be strengthened and more generalisable if both HRR and (HF-)HRV measures had been acquired. However, capturing both measures in ~1600 subjects would have required Holter recordings to be made on a separate occasion from the exercise test day across multiple centers, thereby increasing the complexity of the study substantially. The need for repeat attendance and more complex study design increases the risk of drop-out/attrition, a particular concern given the demographic of our study population. (Sharma et al., 1986) We thus judged that increasing the complexity of the study would have jeopardised achieving the sample size required for a meaningful assessment of the relationship between parasympathetic measures and systemic inflammation. Additional measures of sympathetic activity are also necessary, such as muscle sympathetic nerve activity, (Adlan et al., 2016) to confirm the relative autonomic contributions identified in this population. The measurement of phasic HRV, including HF-HRV, during exercise-evoked alterations in heart rate using this CPET approach may also help identify more readily accessible measures that correlate with markers of systemic inflammation. Additional measures of inflammation, including plasma IL-6, TNF, and leukocyte myeloperoxidase may contribute further insights. In-depth

psychologic assessment to detect overt, subclinical and/or untreated depression and/or anxiety could also enhance our understanding of these important psychological influence on autonomic function.

Conclusions

Using HRV-independent measures of autonomic function evoked by exercise, impaired parasympathetic (vagal) function appears to predominantly contribute to systemic inflammation. Identifying this link in humans adds significant translational weight to laboratory work and reveals a potentially modifiable autonomic phenotype that may be amenable to pharmacologic and non-pharmacologic interventions.

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Figure Legends.

Figure 1. Preoperative systemic inflammation, stratified by quartiles of delayed heart rate.

A. Measurement of anticipatory heart rate, during unloaded pedaling (warm-up period) of CPET.

B. NLR presented by quartiles of anticipatory heart rate.

C. Measurement of heart rate recovery after cessation of exhaustive exercise.

D. Heart rate recovery values, presented by quartile.

E. NLR, across quartiles of heart rate recovery shown in D.

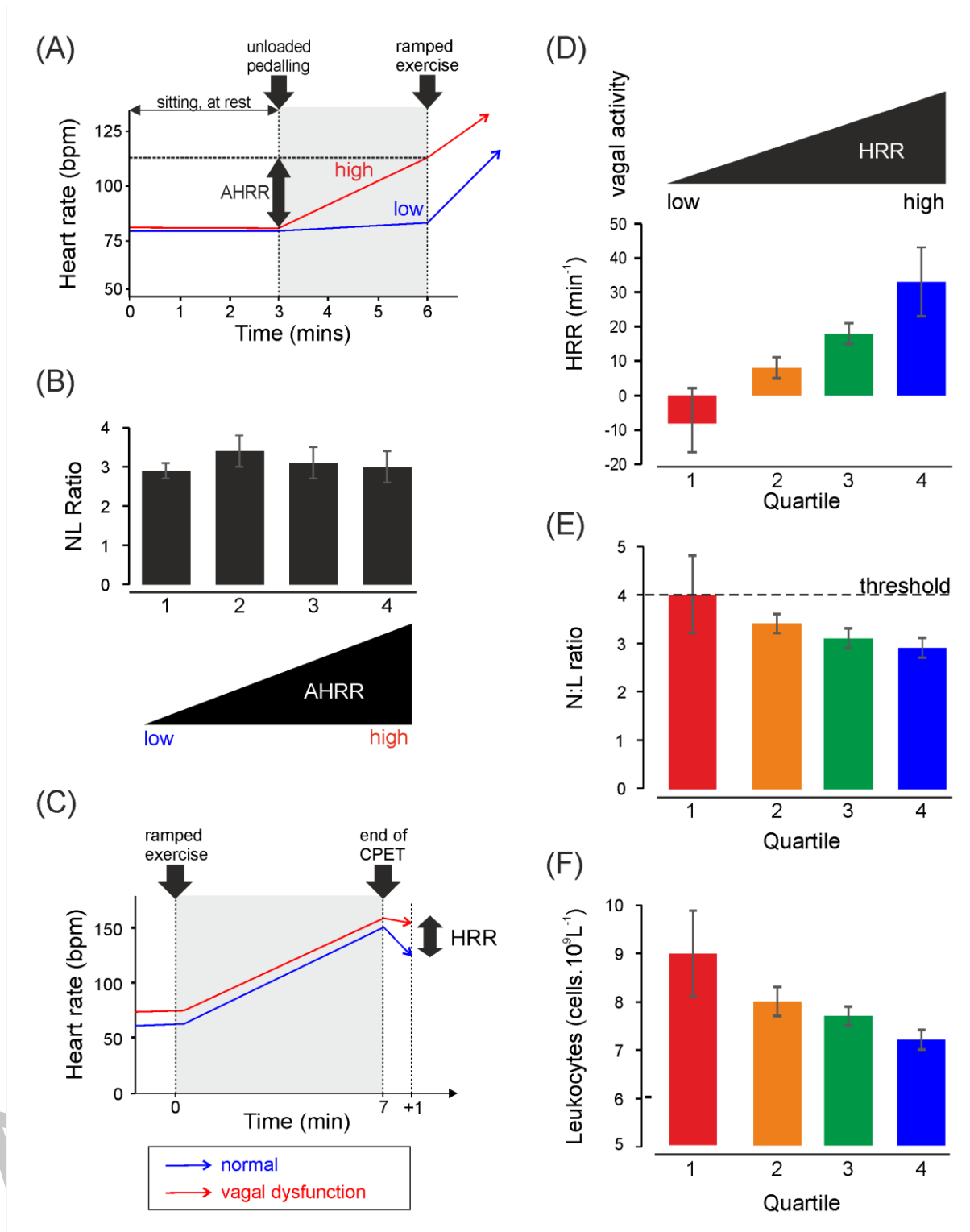F. Total leukocyte count, across quartiles of heart rate recovery shown in D.

Table 1: Subject characteristics.

	Overall	HRR>12	HRR≤12	P value
Number	1624	977	647	
Age (years)	65±14	63±14	69±12	0.001
Male (n, %)	1104 (71%)	673 (68.9%)	431 (66.6%)	0.48
Body mass index (kg.m^{-2})	27.2±5.2	26.9±4.9	27.5±5.7	0.02
Estimated GFR	77±19	79±18	73±20	0.001
Albumin (g.dL^{-1})	43±4	44±4	43±4	0.11
Haemoglobin (g.L^{-1})	132±18	133±18	128±19	0.001
Diabetes mellitus (n, %)	118 (7.3%)	82 (8.4%)	124 (19.1%)	0.01
Ischaemic heart disease (n, %)	186 (11.4%)	72 (7.4%)	79 (12.2%)	0.001
Cardiac failure (n, %)	93 (5.7%)	44 (4.5%)	49 (7.6%)	0.037
Smoker (n; %)	451 (27.8%)	277 (28.4%)	174 (26.9%)	0.15
Inflammatory disease (n, %)	226 (13.9%)	137 (14.0%)	89 (13.8%)	0.88
Cancer/chemotherapy (n;%)	471 (29%)	291 (29.8%)	180 (27.8%)	0.40
Mean Arterial blood pressure (mmHg)	100±14	100±13	100±15	0.66
Anerobic threshold (ml.kg.min^{-1})	11±3	12±3	11±3	0.01
Resting Heart rate (bpm)	82±16	80±14	85±17	0.001
Anticipatory heart rate rise (bpm)	11±10	11±10	11±10	0.37
Peak Heart rate (bpm)	135±24	141±22	126±24	0.001
Heart rate recovery (bpm)	16±12	23±10	6±7	0.001
Any cardiovascular therapy (n, %)	747 (46%)	385 (39.4%)	362 (56%)	
Beta blocker (n, %)	289 (17.8%)	145 (14.8%)	144 (22.3%)	0.001
Calcium channel blocker	195 (12%)	86 (8.8%)	109 (16.8%)	0.001
Diuretic (n, %)	105 (6.5%)	48 (4.9%)	57 (8.8%)	0.003
Nitrate (n, %)	70 (4.3%)	36 (3.7%)	34 (5.2%)	0.17
Statin (n, %)	320 (19.7%)	176 (18%)	144 (22.3%)	0.08
ACE-I/ARB (n, %)	395 (24.3%)	205 (20.9%)	190 (29.4%)	0.002

Whole population data are presented in the second column, with HRR groups dichotomized by the prognostically significant threshold value of 12 beats.min^{-1} in columns 3 and 4. Data presented as mean (SD), or n (%). ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; GFR: glomerular filtration rate. Inflammatory disease includes rheumatoid arthritis, vasculitidies and inflammatory bowel disease, requiring immunosuppressive drug treatment.

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Highlights

- Experimental models show autonomic regulation of systemic inflammation.

- Autonomic measures, independent of heart rate variability, are required in humans.

- Slower heart rate recovery after exercise quantifies vagal dysfunction.

- Delayed heart rate recovery is associated with chronic inflammatory markers.