

Modeling the Association between HR Variability and Illness in Elite Swimmers

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ABSTRACT

HELLARD, P., F. GUIMARAES, M. AVALOS, N. HOUEL, C. HAUSSWIRTH, and J. F. TOUSSAINT. Modeling the Association between HR Variability and Illness in Elite Swimmers. *Med. Sci. Sports Exerc.*, Vol. 43, No. 6, pp. 1063–1070, 2011. **Purpose:** To determine whether HR variability (HRV), an indirect measure of autonomic control, is associated with upper respiratory tract and pulmonary infections, muscular affections, and all-type pathologies in elite swimmers. **Methods:** For this study, 7 elite international and 11 national swimmers were observed weekly for 2 yr. The indexes of cardiac autonomic regulation in supine and orthostatic position were assessed as explanatory variables by time domain (SD1, SD2) and spectral analyses (high frequency [HF] = 0.15–0.40 Hz, low frequency [LF] = 0.04–0.15 Hz, and HF/LF ratio) of HRV. Logistic mixed models described the relationship between the explanatory variables and the risk of upper respiratory tract and pulmonary infections, muscular affections, and all-type pathologies. **Results:** The risk of all-type pathologies was higher for national swimmers and in winter ($P < 0.01$). An increase in the parasympathetic indexes (HF, SD1) in the supine position assessed 1 wk earlier was linked to a higher risk of upper respiratory tract and pulmonary infections ($P < 0.05$) and to a higher risk of muscular affections (increase in HF, $P < 0.05$). Multivariate analyses showed (1) a higher all-type pathologies risk in winter and for an increase in the total power of HRV associated with a decline SD1 in supine position, (2) a higher all-type pathologies risk in winter associated with a decline in HF assessed 1 wk earlier in orthostatic position, and (3) a higher risk of muscular affections in winter associated with a decrease SD1 and an increase LF in orthostatic position. **Conclusions:** Swimmers' health maintenance requires particular attention when autonomic balance shows a sudden increase in parasympathetic indices in the supine position assessed 1 wk earlier evolving toward sympathetic predominance in supine and orthostatic positions. **Key Words:** SWIMMING, UPPER RESPIRATORY TRACT AND PULMONARY INFECTIONS, MUSCULAR AFFECTIONS, MIXED-EFFECTS LOGISTIC REGRESSION MODELS

International and Olympic swimming competitions can be characterized by a rise in the level of the performances (28,37). Moreover, the higher the performance level, the smaller the differences in performance. For example, during the Rome World Championships in 2009, the mean difference for all the swimming finals was $2.9\% \pm 0.9\%$ between the World Champion and the poorest (8th) performance, whereas for the national championships, this difference was $5.1\% \pm 2.8\%$. In such a competitive context, the training must be optimized to reach the highest level of performance, and the risk of infection must be carefully monitored during the most intensive training periods and

actual competition (12,27,29). For example, the swimmers from the Australian team who fell ill in the 6 wk preceding the Commonwealth Games were found to have a 60% greater risk of turning in a poor performance (29).

Yet, reducing the risk of infection during prolonged and intensive training and competition periods depends on several factors (12,21,29). High-level swimmers such as many international athletes encounter many sources of stress in addition to the physiological and biological stress of intensive training. These include stresses due to environmental conditions (e.g., heat and humidity, altitude, air pollution, and traveling great distances and through several time zones), lifestyle factors (e.g., professional obligations, cohabitating, dietary practices), and psychological factors (e.g., personal and psychosocial factors, competition, and training stresses) (12,21,29). This accumulation of acute and chronic stress factors has been shown to disturb several immune parameters, which, in turn, lowers resistance to common minor illnesses such as upper respiratory tract infection (URTI) (12–14,35).

Several studies have also established that physical and psychological stresses disturb autonomic regulation (2,18,21,25,31). These authors observed disturbances in autonomic

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regulation during periods of long and intensive training overload, manifesting first by a shift in autonomic balance toward sympathetic predominance (sympathetic form of overtraining) (18,21,25,31), which then progressed to complete exhaustion of the neuroendocrine system (parasympathetic form of overtraining) when recovery periods were omitted from the training schedule (2,10,18,21).

Several lines of evidence suggest that autonomic imbalance compromises immune regulation and thus increases the risk of illness. For example, the hypothalamus is known to communicate with the immune system via the autonomic nervous system (4). Lymph organs such as the spleen, lymph nodes, and thymus are innervated by noradrenergic fibers from sympathetic neurons (8) and cholinergic fibers (4). Functionally, sedentary subjects with autonomic imbalance characterized by sympathetic predominance were found to be predisposed to gastrointestinal (GI) diseases such as inflammatory bowel disease or active ulcerative colitis (34).

It is generally assumed that sympathetic control promotes the inflammatory response, whereas the parasympathetic arm is protective (22,34). For instance, a study by Marsland et al. (22) provided initial human evidence that vagal activity inhibits the production of proinflammatory cytokines by activated monocytes/macrophages and thus decreases local and systemic inflammation.

However, no study has yet investigated the effects of disturbed autonomic nervous activity on the incidence of infection in elite athletes under the intense stress of training and competition.

This study tested the hypothesis that a shift in autonomic balance toward sympathetic predominance would be associated with a higher risk of infection. The presence of infection and variations in autonomic activity as assessed by HR variability (HRV) were thus assessed weekly in 18 elite swimmers during a 2-yr period.

MATERIALS AND METHODS

Subjects. Eighteen elite swimmers (10 men and 8 women; 7 elite international and 11 national) aged 19–30 yr were followed longitudinally weekly between 2003 and 2005 (1508 wk of observation for the whole cohort). The study was approved by the institutional review board of the host site, and written informed consent was obtained from all athletes. These athletes all trained in the same location and followed the same training program.

Infections and affections. The study was conducted in two Olympic preparation centers. Both centers have a medical service located 500 m from the pool. The same two physicians followed the swimmers during this study. These two physicians developed the questionnaire that was used to document all URTI, pulmonary, GI, gynecological, and urological infections and all neurological symptoms and muscular affections (MA). The questionnaire was derived from the WURSS-44 and the questionnaire of Fricker et al.

(9). On a weekly basis, the physicians thus documented the following symptoms: for upper respiratory infections = sneezing, stuffy nose, runny nose, hoarseness, sore throat, sinus pain, sinus pressure, sinus drainage, swollen glands, ear infection, ear ache, plugged ear, ear discomfort, watery eyes, eye discomfort, headaches, sweats, chills, feeling feverish, feeling tired, irritability, and feeling depressed; and for pulmonary infections = chest congestion, chest tightness, cough, and sputum. The term MA referred to the following: muscle injury (violent pain requiring exercise cessation), pulled muscles (muscle pain during exercise insufficient to stop exercise), tendinopathies (tendon pain with swelling and altered function), delayed-onset muscle soreness persisting >24 h after training, shoulder pain syndrome, and knee pain syndrome. Upper respiratory tract and pulmonary infections (URTPI), MA, and all-type pathologies (AP) were only recorded if the swimmer showed signs or symptoms for >48 h, required medication, and missed at least one training session as a result of illness. A recurring illness was defined as “any upper respiratory tract or pulmonary infections, muscular affections, or all-type pathologies occurring” within 1 wk of a previously recorded episode and was not retained for analysis (9,32). At the appearance of any signs or symptoms, the swimmers were immediately (within 1–6 h) seen by one of the two physicians for a complete clinical examination. Once a diagnosis was made, the swimmer was asked to complete the questionnaire daily during the period of illness. For each episode of illness, the following indices were noted: type, duration (number of days), and peak severity (mild = no change in training program, moderate = training program modified, severe = complete cessation of training). An illness was defined and taken into account for the study when a swimmer reported one or more signs or symptoms on two or more consecutive days or when the severity was rated as either moderate or severe (9).

For statistical reasons (small samples, rare events), the infections were grouped into three responses of primary interest for physicians and trainers: URTPI, MA, and AP.

HRV analysis. All tests were conducted every Monday at 9 a.m. in identical conditions. The swimmers did not train the day before testing to avoid the effects of exercise on the test results. They were also instructed not to ingest any medication, tea, or coffee before the test.

After a 15-min rest, testing began, with each test lasting 16 min: 8 min in supine position (SUP) and 8 min in orthostatic position (OR). Recordings made during the last 6 min of each position were retained for analysis. The time between two consecutive R waves of the recorded cardiac electrical activity (R–R interval) was measured with a Polar S810 HR monitor (Polar, Kempele, Finland).

The HR monitor signal was transferred to the Polar Precision Performance Software, version 4.03.040 (Electro Oy, Kempele, Finland), and the R–R intervals were exported under ASCII format. Before HRV analysis, raw R–R intervals from Polar S810 recordings were edited to discriminate error caused by S810 acquisition, nonsinus beats, or artifacts. S810

artifacts were edited using the automated default protocols in the Polar software. This software corrected for artifacts using an error filter and beat protection zone function. A moderate filter power set at a minimum beat protection of six beats per minute was used. After removal of abnormal intervals, the Polar software linearly interpolated the removed intervals using system-specific algorithms. Each data file was again visually inspected for artifacts, which were manually corrected. The signal was then considered to be normal and to provide normal-to-normal (N–N) intervals. The stationarity of each R–R series was assessed with the paired *t*-test for equality of means and the Levene test for equality of variances adapted to paired data. Samples characterized by means and variances that varied over time were excluded from the study (7.5% of the total data). The corrected files were then transferred under ASCII format to the Nevrokard HRV software (Nevrokard; Medistar, Ljubjana, Slovenia).

An analysis of the R–R interval recordings was made with the Poincare method, which consists of plotting the length of each R–R interval against the length of the previous R–R interval. SD1 and SD2 are two standard Poincare plot descriptors (2). SD1 is a measure of instantaneous variability (successive beats) and is taken as an indicator of parasympathetic activity, whereas SD2 represents long-term variability and indicates both parasympathetic and sympathetic activities (2).

Two R–R segments of 360 s were selected during the last 6 min in the two positions: orthostatic and supine. These 360-s segments were detrended by interpolation of a polynomial function adjusted on a sliding window of 30 R–R intervals by an algorithm minimizing the residual sum of squares between the simulated curve and the experimental curve. The 30-point window size was chosen to achieve the correct trade-off between reducing noise and avoiding the introduction of bias. The new function (R–R interval vs time) adjusted by the polynomial function was thus resampled at 2 Hz to obtain equidistant data (720 points). The segment was then windowed using a Hanning window to reduce the spectral leakage resulting from edge effects when using finite data periods. On this resampled R–R interval series, the first “integer power of 2” points were selected (512 points) on which the fast Fourier transform was applied. The spectral power was measured by frequency bands in milliseconds-hertz (ms·Hz) according to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996).

The following HRV indices were computed: total power and spectral power in the low-frequency (LF; 0.04–0.15 Hz) and high-frequency (HF; 0.15–0.40 Hz) bands expressed in absolute values (ms^2) and normalized units (HFnu, LFnu), which represent the relative value of each power component in proportion to the total power minus the very low frequency component (≤ 0.01 –0.04 Hz).

The HF component primarily reflects the variability of vagal outflow (i.e., parasympathetic activity) to the heart,

whereas the LF component reflects both sympathetic and parasympathetic influences. However, LF power often contains a substantial amount of parasympathetic influence, which would explain why HF power and LF power are frequently directly correlated (as seen in our subjects) and why decreased levels in HF power and LF power both predict cardiovascular outcome in the same direction (33). The LF/HF power ratio quantifies the sympathovagal balance, with relatively higher ratios indicating relatively more sympathetic than parasympathetic modulation of the heart rhythm (33).

Statistical analysis. The three outcome variables were the presence or absence of URTPI, MA, or AP (for each subject at each observation time). The explanatory variables were the HRV measures performed during the same week and during the previous week ($w-1$). The adjustment variables were time variables (sport season = 2003–2004 and 2004–2005 and semiseason = winter [from September to March] and summer [from April to July]) and individual characteristics such as age, sex, and competition level.

Analysis was conducted using mixed-effects logistic regression models. Logistic regression is a standard tool for analyzing the dependence of binary variables on explanatory variables. The logistic regression model, which assumes that all observations are independent of each other, is nevertheless not appropriate for analyzing several types of correlated data structures, particularly longitudinal data (i.e., repeated observations within subjects). For analysis of such data, random subject effects can be added into the (fixed-effects) regression model to account for the correlation of the data. The resulting model is a mixed model including the usual fixed effects for the explanatory variables (thus, the effects common to the population are estimated using all the data) plus the random effects (to take into account individual heterogeneity) (38).

In particular, in random intercept models only, the intercept parameter is assumed to vary independently from one subject to another according to a common distribution. Logistic random intercept models were fitted using the NLMIXED procedure of SAS version 9.1 (Cary, NC). Coefficients were interpreted in terms of the odds ratio of an average subject.

The recommendation is to rescale mixed models with random effects, which are expected to have small variability, to enlarge the covariance parameters and thus prevent algorithm convergence problems (38). Therefore, we expressed each HRV variable as a percentage of its maximum during the study period. This rescaling also facilitated comparison of HRV data from one individual to another.

A univariate analysis was performed: the time variables and individual characteristics were included alone as single fixed effects in a logistic random intercept model.

After the univariate preselection of variables, multivariate analysis was performed. All pertinent combinations of HRV indexes and significant adjustment variables were included in the models as fixed effects, as well as a subject-specific intercept.

TABLE 1. Incidence of infectious disease during the study period.

Infection or Affection Type	Occurrence	Pct.
URTPI	109	7.23
GI	19	1.26
Urogenital	8	0.53
Neurological	3	0.20
Muscular	132	8.75
All types	255	16.91

During the 1508 wk of observation, we counted the number of weeks in which each type of infection or affection was reported. The weeks characterized by infection/affection were then added to give the category of all types of infection/affection combined.

For interpretability reasons, the HRV data from the supine and orthostatic positions were not included simultaneously in the models. Interactions were not statistically significant and were not included.

Model selection relied on the Akaike Information Criterion (AIC). Among the models with the smallest AIC, those with significant variables were selected. A significance level of 0.05 was used for all tests. In further analyses, receiver operating characteristic curves and the associated area under the curve (AUC) with its 95% confidence interval (CI) were calculated for each retained model to express the discriminating power of each model. Finally, a subject influence study was performed.

RESULTS

Time variables and individual characteristics.

Table 1 shows the percentage for each category of infection or affection for the 1508 wk of observation.

Table 2 shows the effects of the time variables and the individual characteristics on the three outcome variables. The number of occurrences of each variable is also presented in terms of sex, competition level, season, and semiseason. The risk of URTPI was significantly lower for the international swimmers compared with the national swimmers. A significant negative effect of winter compared with summer was found for URTPI, MA, and AP, especially for ear, nose, throat or pulmonary infection.

Modeling results. Eight HRV variables were quantified in supine and orthostatic positions. Table 3 summarizes the average HRV measures for each position as a function of the occurrence or absence of infection.

Univariate analyses showed that the increase in the parasympathetic indexes in SUP assessed 1 wk earlier was linked to a higher risk of URTPI (increase in HF and SD1, $P < 0.05$, AUC = 0.69, 95% CI [AUC] = 0.64–0.75), and to a higher risk of MA (increase in HF, $P < 0.05$, AUC = 0.78, 95% CI [AUC] = 0.72–0.85).

Concerning the results measured during the same week, the risk of MA in SUP was statistically linked with an increase in sympathetic (SD2) ($P < 0.05$, AUC = 0.73, 95% CI [AUC] = 0.68–0.78) and parasympathetic (HF) autonomic regulation indexes ($P < 0.05$, AUC = 0.67, 95% CI [AUC] = 0.59–0.75), as well as a gain in the LF/HF power ratio ($P < 0.05$). Concerning the OR position, our results showed that a decrease in HFnu was associated with an increased risk of MA measured during the same week, with excellent model-discriminating power ($P < 0.05$, AUC = 0.83, 95% CI [AUC] = 0.76–0.89). We also found that a gain in the LF/HF power ratio was statistically linked to an increase in URTPI ($P < 0.05$, AUC = 0.68, 95% CI [AUC] = 0.61–0.75) and MA ($P < 0.05$, AUC = 0.74, 95% CI [AUC] = 0.69–0.79).

Table 4 presents the parameter estimations for the three selected multivariate models. All models outline individual variability, with a significant random intercept SD ($P < 0.05$).

AP. Multivariate analyses showed a higher AP risk in winter (model 1 in Table 4) and for an increase in the total power of HRV associated with a decline in SD1 in SUP ($P < 0.05$, AUC = 0.7, 95% CI [AUC] = 0.64–0.76).

In OR position in winter, the decrease in HF during $w-1$ increased the risk of AP AUC = 0.8, 95% CI [AUC] = 0.73–0.85; model 2 in Table 4).

MA. Increased LF and decreased SD1 in OR position were associated with an increased risk of MA (AUC = 0.89, 95% CI [AUC] = 0.83–0.96; model 3 in Table 4).

DISCUSSION

The main results of this study were the following: 1) In winter, national-level swimmers showed a greater risk of pathology than international-level swimmers. 2) The weeks that preceded the appearance of URTI and pulmonary infection but also MA were characterized by an increase in

TABLE 2. Incidence (n), odds ratio, and 95% CI for the association between adjustment variables and pathologies for the 1508 wk of follow-up of 18 subjects.

Variable	AP		URTPI		MA	
	n	Odds Ratio (95% CI)	n	Odds Ratio (95% CI)	n	Odds Ratio (95% CI)
Age		0.96 (0.88–1.05)		0.96 (0.86–1.07)		0.95 (0.80–1.13)
Sex						
Female	138	1.16 (0.60–2.25)	52	0.91 (0.42–1.99)	79	1.25 (0.37–4.24)
Male	117		57		53	
Competition level						
International	74	0.65 (0.34–1.25)	21	0.37 (0.19–0.72)*	44	0.99 (0.28–3.46)
National	181		88		88	
Season						
2003–2004	152	0.91 (0.65–1.26)	80	1.72 (1.04–2.85)*	56	0.41 (0.26–0.64)*
2004–2005	103		29		76	
Semiseason						
Summer	64	0.25 (0.18–0.36)*	24	0.25 (0.15–0.42)*	36	0.31 (0.20–0.49)*
Winter	191		85		96	

* $P < 0.05$.

TABLE 3. HRV data (ms²) in the supine and orthostatic positions as a function of AP presence or absence.

HRV Variable	Position	Infection Presence			Infection Absence		
		n	Mean	SD	n	Mean	SD
SD1	SUP	108	58.4	30.6	311	63.2	35.3
	OR	74	20.9	15.8	209	22.7	16.8
SD2	SUP	108	124.3	60.0	311	120.9	57.4
	OR	74	94.2	54.0	208	97.6	51.4
PT	SUP	108	28,760.2	62,417.0	311	25,564.2	50,243.4
	OR	75	23,130.5	45,939.6	212	27,343.9	59,571.8
VLF	SUP	108	23,743.0	60,007.9	311	20,282.6	49,116.0
	OR	75	20,807.9	44,762.1	212	24,761.5	58,556.5
LF	SUP	108	2551.7	2223.7	311	2560.4	2436.5
	OR	75	1930.7	1959.7	212	2108.0	2235.9
HF	SUP	108	2454.3	2470.1	311	2722.9	3213.4
	OR	75	399.9	647.8	212	474.4	963.0
LF/HF	SUP	108	1.5	1.3	311	1.5	1.5
	OR	74	11.6	10.4	211	12.2	12.2
HFnu	SUP	108	47.1	17.4	311	48.0	16.8
	OR	75	14.0	12.8	212	15.3	14.0

VLF, very low frequency.

autonomic parasympathetic activity in supine position. Conversely, in orthostatic position and in winter, the weeks that preceded the appearance of AP were characterized by a drop in parasympathetic activity. 3) During weeks characterized by URTI and pulmonary infection, a shift was noted in the autonomic balance toward sympathetic predominance in supine position and a drop in parasympathetic drive in orthostatic position. And 4) in winter and in orthostatic position, a drop in parasympathetic drive associated with an increase in sympathetic drive was linked to an increased risk of MA.

During and after intensive and stressful physical work (e.g., long and intensive competitive trials, long-term habitual intense exercise, altitude training), studies have shown both a shift in autonomic balance toward sympathetic predominance (25,31) and immunosuppression (12,13,15), possibly linked (12,14,16) or not (15,17) to an increased risk of pathology.

To our knowledge, no study has yet associated the risk of illness with autonomic functioning as reflected by HR variability. We hypothesized that a shift in autonomic balance toward orthosympathetic predominance would increase the risk of pathology.

In agreement with earlier studies of athletes exposed to prolonged and/or intense stress, such as training overload or competition (9,12,13,24,31,32,35), URTI were the most

frequent pathologies observed in this study. Only 1 of the 18 swimmers did not fall ill during the 2-yr study period, and 118 of the 1508 wk were characterized by illness (7.82% of the total observation period). In comparison, Spence et al. (32) observed 21 URTI episodes in 20 elite triathletes and cyclists studied for 5 months. Fricker et al. (9) reported that 42 wk (17.5%) were characterized by URTI episodes in 15 elite runners studied for 240 wk. Gleeson et al. (15) observed 22 elite swimmers for 12 wk of summertime training in 1999 and diagnosed at least one infection in 10 of the swimmers (45% of the study population).

An increased risk of URTI has been associated in athletes (32), and particularly swimmers (13–15), with a decrease in systemic antibodies (12,13,21) and laryngopharyngeal mucosal antibodies like salivary immunoglobulin A (S-IgA) (12–14). Some studies of the laryngopharyngeal mucosa questioned a direct causality between S-IgA concentration and the risk of URTI (12,15,16). These authors hypothesized that the minor drop in general and local immunity induced by intensive training and stress did not directly cause illness but instead lowered resistance to potential viral (16) or nonviral pathogens, thus increasing the risk of URTI (12,17,32).

Lower viral resistance would explain the higher risk of infection in the winter observed in our study and often reported in the epidemiologic literature (3) because winter is

TABLE 4. Estimations of the multivariate models selected according to the statistical AIC.

Model	Outcome Variables	Explanatory Variables	Estimation (SD)	P	Random Effects, P	AUC 95% CI
1	AP	Intercept	-0.414 (0.379)	0.290	0.029	0.70 (0.64–0.76)
		TP in SUP	0.013 (0.005)	0.022		
		SD1 in SUP	-0.015 (0.007)	0.036		
		Summer	-0.999 (0.321)	0.006		
2	AP	Intercept	-0.630 (0.344)	0.084	0.005	0.79 (0.73–0.85)
		HF in OR w-1	-0.015 (0.007)	0.052		
		Summer	-1.188 (0.366)	0.005		
3	MA	Intercept	-1.950 (0.771)	0.022	0.007	0.89 (0.83–0.96)
		LF in OR	0.039 (0.015)	0.018		
		SD1 in OR	-0.044 (0.020)	0.039		
		Summer	-1.664 (0.678)	0.026		

Model 1: Probability of AP presence as a function of total power of HRV in supine position (TP in SUP) and instantaneous variability in supine position (SD1 in SUP) adjusted by semiseason (reference category: Summer), number of observations $n = 419$, for 18 subjects.

Model 2: Probability of AP presence as a function of the high-frequency component of HRV in orthostatic position assessed 1 wk earlier (HF in OR w-1), $n = 288$, for 18 subjects.

Model 3: Probability of MA presence as a function of the low-frequency component of HRV in orthostatic position (LF in OR) and instantaneous variability in orthostatic position (SD1 in OR) adjusted by semiseason, $n = 283$, for 17 subjects.

characterized by a surge in viral outbreaks that increase the risk of infection, particularly in cases of lowered immune defense (3).

The frequency of GI symptoms (1.26% of the reported illness) was much lower than that observed in runners during intensive training (9,15,24). In fact, twice as many GI infections were observed during running (reported by up to 20%–50% of runners during heavy exercise) than during swimming (24). These findings were explained as the result of less mechanical bouncing during swimming, which has limited up and down movements (24). Although splanchnic blood flow is greatly reduced during high-intensity running, leading to ischemic damage associated with inflammatory response (24), the horizontal position of swimming prevents this phenomenon.

Of particular interest was the finding that pathology risk was lower in the international swimmers than in the national swimmers, despite similarities in age and training. Epidemiological studies will need to confirm this finding of lower susceptibility to pathology in high-level athletes and to determine whether it is genetically determined, as observed in other populations (36), and/or due to the athletic lifestyle (emphasis on sleep quality and nutrition, immunonutrition supplementation) (12,23).

To our knowledge, this is the first report to point out a relationship between autonomic activity and the pathology potential in high-level athletes.

The interpretation of these results remains speculative because the autonomic control of potentially infected systems can only be inferred from the measure of HR variability (22). Future research will have to highlight the synergy between cardiac autonomic regulation and the autonomic regulation of respiratory, GI and muscular systems, as seen in the studies on the autonomic regulation of three functional domains: sudomotor, cardiovagal, and adrenergic (20). Moreover, we did not measure immunological or neuroendocrine parameters, although this might have provided insight into the mechanisms of action of the autonomic regulation of immune system activity.

The results of the present study suggest a biphasic time-dependent relationship between autonomic activity and URTI and pulmonary infection. The weeks that preceded the appearance of URTI and pulmonary infection but also MA were characterized by an increase in autonomic parasympathetic activity in supine position.

This period preceding the clinical expression of the illness could correspond to the incubation phase, for which the mean duration was estimated to be 5 d, of URTI and pulmonary infections (3). During this first asymptomatic incubation phase, the increase in the vagal pathway could play a protective role by modulating the magnitude of early immune responses to inflammatory stimuli (3,22). Indeed, it is hypothesized that afferent vagal neurons relay sensory information regarding early inflammatory activity to the brain, which results in reflexive activation of the efferent vagal fibers leading to the suppression of proinflammatory

cytokine release (39). This efferent pathway, termed the “cholinergic antiinflammatory pathway,” is proposed to play an important role in preventing excessive inflammatory responses and maintaining health (19,39). Experimental animal studies also showed that the increase in parasympathetic autonomic activity could counterbalance an excessive sympathetic activity, which downregulates the immune responses to viral and cellular antigens (30).

During the second phase corresponding to the symptomatic clinical expression of infections, the subjects of the present study were characterized by a shift of the autonomic balance toward a sympathetic dominance. The symptomatic phase shows a multiplication and then a scattering of viral and bacterial exogenous pathogenic agents into the bloodstream. These pathogenic agents activate the macrophages that produce endogenous pyrogens (such as the proinflammatory cytokines interleukin 1 β , tumor necrosis factor α , and interleukin 6) and migrate into the bloodstream to the endothelial and perivascular cells of the blood–brain barrier, inducing the coding of a mediator, prostaglandin E₂ (30). In various areas of the hypothalamus and brainstem, prostaglandin E₂ mediates different components of the acute-phase reaction such as the thermogenesis activation by the sympathetic nervous system (30).

Other investigators have found that disturbances in immune–neuroendocrine regulation and direct autonomic neural circuits can induce immune system alterations in the laryngopharynx (5,25,32). For example, nonviral infections of the laryngopharynx were more frequent when the mucosal lining of the nasopharynx or the normal comensal flora were altered owing to autonomic-dependent vasomotor modifications (32). Animal studies have shown that long-term removal of parasympathetic (26) or sympathetic (5) nerve impulses in the submandibular glands reduced S-IgA concentration in saliva.

In active men, exercise intensity can provoke a shift toward orthosympathetic predominance in the salivary glands, which disturbs mouth and nasopharyngeal ecology (1). When S-IgA lowers and the mucus membranes dry out, bacteria proliferate, predisposing to mucosal damage and inflammation, which could compromise resistance to common minor illnesses, such as URTI (5,12,26).

This type of autonomic imbalance in elite swimmers could increase the effect of other risk factors, such as mucosal irritation caused by hyperventilation, high exposure to nonvirulent and virulent pathogenic and opportunistic microorganisms concentrated in the water surface film, and repeated exposure to chemical disinfectants like chlorine, which can cause mucosal irritation and inflammation (12).

The multivariate analysis revealed that the drop in parasympathetic control of HR and the concomitant rise in the orthosympathetic regulation were linked in winter to an increased risk of MA.

In orthostatic conditions similar to our conditions, the increase in LF power indicated mostly sympathetic control predominance because cardiac autonomic balance favors

vasomotor control through sympathetic dominance over parasympathetic influences (11,33).

An autonomic profile characterized by decreased parasympathetic regulation and higher sympathetic input has been suggested as one of the first responses to an overtraining stimulus, as previously reported for high-intensity training (10). This response, termed sympathetic overtraining syndrome, is characterized by complete abolition of the sympathetic regulation of skeletal muscle as manifested by a loss of strength and power and delayed muscular recovery (10,40).

Fry et al. (10) investigated the mechanisms by which this type of overtraining lowers performance and muscle recovery. They showed in eight overtrained weight-trained men that intense muscle stress provoked a 49% increase in nocturnal urinary epinephrine concentration and a decrease in the density of muscular β_2 -adrenergic receptors, indicating desensitization. They hypothesized that desensitization of β_2 -adrenergic receptors due to sympathetic overtraining affected the mitogen-activated protein kinases, a complex that relays extracellular stimuli to the nuclear domain of the muscle cell.

Moreover, MA like delayed-onset muscle soreness, which is characteristic of cell damage, cause local tissue inflammation linked to the production of inflammatory mediators (6,7). Recent experimental studies have shown that local inflammation marked by the increase of the inflammatory markers such as C-reactive protein and interleukin 6 can be regulated by autonomic influences through the cholinergic antiinflammatory pathway induced by vagal nerve stimulation (39).

Many reports have emphasized that exposure to multiple stressors (physical, psychological, and environmental) acting in concert may have interactive or cumulative effects that disturb the neuroendocrine and immune systems and increase the risk of infection (12,17). For the first time to our knowledge, our study presents statistical evidence of the effect of several variables, such as wintertime, swimming level, and a shift in autonomic balance toward sympathetic predominance, on the risk of infection.

This study has some limitations. First, we were unable to measure biological parameters of mucosal or general

immunity and inflammatory markers because of the long study period and the high number of subjects. Such measures would have provided insight into the mechanisms of autonomic regulation of immune and neuroendocrine systems and the effect on the risk of infection (17). Without these measures, our hypotheses remain essentially speculative. Second, we did not perform analyses to determine the cause of illness and thus could not distinguish pathogens from inflammatory causes, as suggested by Spence et al. (32).

Several tools have been proposed to monitor the effects of physical and psychological training stresses in high-level athletes and to prevent the risks of overtraining and infection (12,29,23). These include regular measures of maximal HR, the maximal blood lactate level corresponding to the perception of effort, plasma cortisol concentration, and fatigue and mood state as assessed by questionnaire (12,21).

The results of this study argue that HRV is a rapid and noninvasive tool to indicate autonomic function, which provides complementary information that may help to reduce the risk of infection in elite swimmers. Weekly HRV monitoring would indicate a drop in parasympathetic regulation, which increases the likelihood of pathology. The clinical recommendation in the case of signs or symptoms of illness and recovery from illness is to avoid or attenuate high-risk periods such as winter, overtraining with increased training volume and intensity (21,25,35), competition, travel through several time zones, and altitude training (31), all of which may induce a shift in the autonomic balance toward orthosympathetic predominance. Another recommendation is to intensify medical surveillance and institute prophylactic measures when autonomic balance shows a sudden increase in parasympathetic indices in the supine position, which progresses some days later toward sympathetic predominance in the supine and orthostatic positions.

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