# Peripheral-Arterial Tonometry for Assessing Endothelial Function in Relation to Dietary Habits

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**Background:** Peripheral-arterial tonometry (PAT) provides, with good reproducibility, measures of nitric oxide–mediated endothelial response, which correlate with flow-mediated dilation (FMD) findings obtained by brachial artery ultrasound. Few data about the ability of exploring endothelial function by PAT in relation to dietary habits are available. The aim of this study was to evaluate natural logarithm of reactive hyperemia index (lnRHI) in subjects referred for primary prevention, in relation to classic risk factors, in particular to adherence to Mediterranean diet and red wine consumption.

**Methods:** The study population was composed of 95 consecutive clinically stable subjects in primary prevention for cardiovascular diseases. All subjects underwent medical questionnaire, clinical examination, and PAT for endothelial function evaluation.

**Results:** A significant inverse correlation between lnRHI values and body mass index ($r = -0.284$; $P = 0.022$) was found. We described a gradual reduction in lnRHI values, corresponding to the increase in the number of risk factors (0.75 [0.31–1.26], 0.66 [0.25–0.97], 0.63 [0.37–1.19], 0.48 [0.32–0.71], 0.43 [0.31–0.91], respectively, for none, 1, 2, 3, and 4 cardiovascular risk factors; $P = 0.004$). A significant positive correlation between score of adherence to Mediterranean diet and lnRHI values was found ($r = 0.307$; $P = 0.002$). Higher adherence to Mediterranean diet was found in subjects with lnRHI values greater than 0.40 in comparison to others (39 [27–50] vs 33 [28–45], respectively; $P = 0.064$). The lnRHI values were significantly higher in regular drinkers in comparison to nonregular drinkers (0.46 [0.25–0.83] vs 0.70 [0.32–1.26], respectively; $P < 0.0001$).

Relationship between reactive hyperemia index and red wine consumption remained statistically significant even after adjustment for age, sex, body mass index, smoking habit, hypertension, and adherence to Mediterranean diet.

**Conclusions:** Our findings strengthen the ability of PAT to evaluate alterations of endothelium response to ischemia, in relation to physiological and clinical conditions, so indicating possible usefulness to optimize and personalize risk stratification.

**Key Words:** endothelial function, cardiovascular risk factors, peripheral-arterial tonometry, Mediterranean diet, red wine consumption

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Several studies demonstrated that endothelial function is associated with the occurrence and the progression of atherosclerotic lesions and is associated with fatal and nonfatal vascular events.

Endothelial function has been evaluated by using flow-mediated dilation (FMD), a method requiring demanding equipment and trained operators.[1]

Nowadays, a new system provides the opportunity of exploring endothelial function by a noninvasive assessment of peripheral-arterial tonometry (PAT) at digital arteries. Assessment of vascular function with PAT involves measuring pulse amplitude in the fingertip at rest and following the induction of reactive hyperemia.[2]

Several studies showed that PAT technology provides, with good reproducibility,[3] measures of nitric oxide–mediated endothelial response[4] and that these results correlate with FMD findings obtained by brachial artery ultrasound.[5–8] In particular, Dhindsa et al.,[8] who evaluated endothelial function in apparently healthy subjects, similarly to our study population, showed an association between PAT and FMD values, suggesting that it may be an alternative approach to FMD. Nevertheless, these 2 methodologies evaluate different physiological aspects related to microvascular and macrovascular reactive hyperemia, and associations among different measures were present, but modest.[8] These results suggest that different physiological mechanisms may be involved in changing different measures of vascular reactivity, showing that PAT is not a substitute of FMD.

Recently, new data investigated associations between reactive hyperemia index and intravascular ultrasound assessment–evaluated coronary plaques, evidencing a greater risk of coronary events in patients with abnormal reactive hyperemia index (RHI) values and a plaque structure more prone to rupture.[9] To evaluate the role of endothelial response in atherosclerotic progression, further data were provided by assessing the relationships between endothelial dysfunction and coronary artery disease in diabetic and nondiabetic patients.[10]

Alterations in endothelial response to induced ischemia by using FMD were investigated in determined classic risk factors in relation to dietary composition.[11] Few data about the ability of exploring endothelial function by PAT in relation to dietary habits are available.

The aim of this study was to evaluate natural logarithm of RHI (lnRHI) in subjects referred for primary prevention, in relation to classic risk factors, in particular to adherence to Mediterranean diet and red wine consumption.

## MATERIALS AND METHODS

### Study Population

The study population was composed of 95 consecutive clinically stable subjects in primary prevention for cardiovascular diseases, referred to our center. The present study is actually the follow-up study of a previous epidemiological study, "Alimentazione per la Salute e la Prevenzione di Malattia," supported by the Italian Minister of Health and previously published.[12] All subjects

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**TABLE 1.** Baseline Characteristics of Study Population (n = 95) and Sex-Specific Analyses

| Variable | Females, n = 45 (47.9%) | Males, n = 40 (42.1%) | Total Population, n = 95 (100%) |
|---|---|---|---|
| Age, median (range), y | 63 (25–88) | 67 (25–86) | 65.5 (25–88) |
| BMI (median, range), kg/m$^2$ | 23.6 (18.7–34.2) | 24.6 (21.1–29.4) | 23.5 (18.7–34.2) |
| Score for adherence to Mediterranean diet, median (range) | 39 (28–50) | 38.5 (27–50) | 39 (27–50) |
| Current smokers, n (%) | 10 (22.3) | 14 (35) | 24 (36.9) |
| Hypertension, n (%) | 30 (66.7) | 23 (57.5) | 53 (55.8) |
| ACEi/ARBs, n (%) | 24 (53.3) | 22 (55.0) | 46 (48.4) |
| Calcium antagonists, n (%) | 6 (13.3) | 6 (15.0) | 12 (13.0) |
| β-Blockers, n (%) | 7 (15.6) | 3 (7.5) | 10 (10.5) |
| Dyslipidemia, n (%) | 18 (40.0) | 11 (27.5) | 29 (30.5) |
| Statin therapy, n (%) | 17 (37.8) | 10 (25.0) | 27 (28.4) |

ACEi indicates angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers.

underwent vascular function assessment; this evaluation was part of the clinical protocol of our center. They underwent only noninvasive procedure. All subjects underwent medical questionnaire and clinical examination, to rule out any clinically relevant problem, and PAT for endothelial function evaluation.

The presence of cardiovascular risk factors was assessed in each subject: male sex, hypertension (systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or taking antihypertensive medication), hyperlipidemia (total serum cholesterol level 200 mg/dL or taking lipid-lowering medication), diabetes mellitus (treated with an oral hypoglycemic agent, insulin, or both, or having fasting glucose levels >126 mg/dL), family history of coronary artery diseases (having first- or second-degree relatives with premature cardiovascular disease), postmenopause, smoking habit, overweight (body mass index [BMI] >25 kg/m$^2$), and dietary habits (expressed as adherence to Mediterranean diet).[13] Dietary habits and daily red wine consumption have been collected by MedDietScore.[13] Amount of red wine was evaluated in number of "wine glasses," corresponding to about 125 mL per glass.

## Reactive Hyperemia by PAT

Endothelial function was measured via PAT values (expressed as lnRHI) according to the previously described method.[2] Peripheral-arterial tonometry signals were obtained using the EndoPAT 2000 device (Itamar Medical Ltd, Caesarea, Israel), a noninvasive technology offering a beat-to-beat plethysmographic recording of the digital arterial pulse-wave amplitude by pneumatic probes, which has been largely validated and used to assess peripheral-arterial tone.[5–8]

The PAT finger probes are 2 thimble-shaped sensor caps that, applying a uniform pressure field and showing a clamp-like effect on the entire surface of the distal phalanx of both fore fingers, continuously measure the pulsatile volume changes. Peripheral-arterial tonometry imparts a consistent counterpressure (70 mm Hg) on the finger, to avoid distal venous distension and inhibit venous pooling and blood stasis, which could otherwise induce a venoarteriolar reflex vasoconstrictor response. Second, the pressure field applied to the finger may also protect against local venous distension relative to the elevated venous pressure in the upper arm during the cuff inflation portion of reactive hyperemia testing.[5,6] Peripheral-arterial tonometry is thus configured to unload arterial wall tension and increase the range of arterial wall motion without inducing potentially confounding vasomotor changes.[7] The finger probe is connected by flexible tubing to isolated volume reservoirs that buffer pressure changes within the probes. The pressure change curves are at the same time filtered, amplified, displayed, and then stored for further analysis, by automatic software.

The PAT assessment protocol provides a 15-minute recording time.[14] After a 5-minute equilibration period, which is used as baseline, the blood pressure cuff, placed at the nondominant

**TABLE 2.** LnRHI Values Distribution (n = 95)

| | Absent | Present | *P* |
|---|---|---|---|
| Male sex | 0.65 (0.25–0.97) | 0.61 (0.31–1.26) | 0.9 |
| Smoking habit | 0.68 (0.25–1.26) | 0.47 (0.31–0.94) | **0.008** |
| BMI >25 kg/m$^2$ | 0.68 (0.25–1.26) | 0.51 (0.31–1.19) | **0.01** |
| Hypertension | 0.75 (0.31–1.26) | 0.58 (0.25–1.19) | **0.016** |
| ACEi/ARBs | 0.65 (0.25–1.19) | 0.58 (0.31–0.96) | 0.8 |
| Calcium antagonists | 0.58 (0.25–0.96) | 0.55 (0.37–1.19) | 0.9 |
| β-Blockers | 0.57 (0.25–1.19) | 0.65 (0.36–0.76) | 0.6 |
| Monotherapy | 0.51 (0.36–0.92) | 0.59 (0.25–1.19) | 0.5 |
| Dyslipidemia | 0.66 (0.25–1.26) | 0.60 (0.31–0.97) | 0.7 |
| Red wine consumption | 0.46 (0.25–0.83) | 0.70 (0.32–1.26) | <**0.0001** |

ACEi indicates angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers.
Statistically significant values were indicated in bold font.

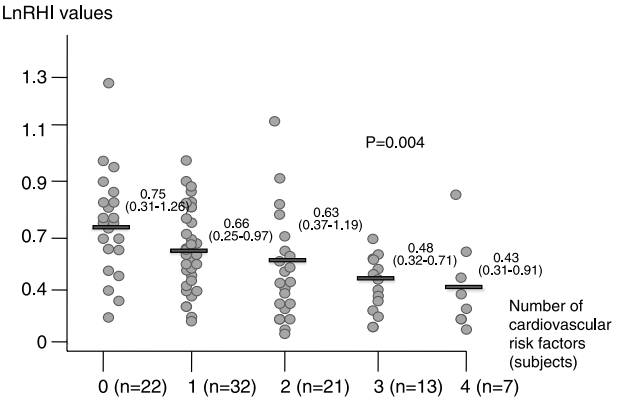


**FIGURE 1.** Relationship between lnRHI values and number of cardiovascular risk factors (n = 95).

arm, was inflated to suprasystolic pressures (about 200 mm Hg) for 5 minutes. The dominant arm serves as control. Then the cuff was deflated, whereas PAT recording continued for 5 minutes. The main outcome measure RHI was automatically calculated by the Itamar software, as the ratio of the digital pulse volume during reactive hyperemia over a 1-minute time interval starting 1 minute after cuff deflation to that at baseline; we converted RHI value in natural logarithm value.[14]

## Statistical Analysis

Statistical analysis was performed with SPSS (Statistic Package for Social Sciences, Chicago, IL) for Windows (version 19). Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as median (range).

The nonparametric Mann-Whitney and Kruskal-Wallis tests were used for analysis of unpaired data. Correlation analysis was measured by using the Spearman correlation test. Univariate and multivariate linear regression tests were used for analyzing relationships between independent factors able to influence RHI values. $P < 0.05$ was considered to indicate statistical significance. Reactive hyperemia index was automatically calculated by the software (Itamar Medical) from pulse-wave amplitude analyses, as previously demonstrated,[15] and then converted in natural logarithm value (lnRHI).

An lnRHI cutoff value (<0.40) has been calculated as the natural logarithm of RHI Natural PAT ratio (PAT ratio = [(Xht / Xho) / (XCT / XCO)] according to the RHI cutoff elaborated by Rubinshtein et al.[14]

# RESULTS

## Baseline Characteristics

Demographic and clinical characteristics of study population, providing sex-specific analyses, are reported in Table 1.

Fifty-three (55.8%) of 95 patients were hypertensive and under good therapeutic control; only 13 patients (13.7%) were treated with 2 or more antihypertensive drugs.

Twenty-nine subjects (30.5 %) were dyslipidemic, and 27 (28.4%) were on statin therapy; all patients were under good therapeutic control. None had diabetes. None had previous adverse cardiovascular events.

Data on adherence to Mediterranean diet are reported in Table 1. Higher adherence score was found in patients with BMI of less than 25 kg/m$^2$ (39 kg/m$^2$ [28–50] vs 36 kg/m$^2$ [27–46]; $P = 0.019$). We did not find significant differences in demographic and clinical characteristics of study population, according to sex. Overweight patients with concomitant smoking habit (15.8%) showed a lower adherence score in comparison to normal-weight and nonsmoker subjects (32 [27–46] vs 39 [28–50]; $P = 0.009$). Lower adherence to Mediterranean diet was observed in dyslipidemic patients in comparison to others (32 [27–48] vs 40 [27–50]; $P = 0.002$).

Regarding the intake of alcoholic beverages, 64 (67.4%) of 95 patients were regular consumers of red wine with meals; among these, the intake of red wine was 1.0 glass per meal for men (1.0 [0.5–2]) and 0.5 glasses per meal for women (0.5 [0.25–1.0]) ($P$ <0.0001). The regular intake of red wine was more prevalent among men than among women (Table 1). We showed no differences in dietary habits and presence of traditional risk factors between regular wine drinkers and nonregular drinkers.

## LnRHI Assessment by PAT

Natural logarithm of reactive hyperemia index median value was 0.65 (0.25–0.97) in women and 0.61 (0.31–1.26) in men ($P = 0.9$). Thirteen (13.7%) of 95 patients showed lnRHI cutoff value less than 0.40. Correlation between lnRHI values and age was not significant ($r = -0.20$, $P = 0.9$).

Natural logarithm of reactive hyperemia index median values related to the presence of cardiovascular risk factors are shown in Table 2.

A significant inverse correlation between lnRHI values and BMI ($r = -0.284$; $P = 0.022$) was found. We described a gradual reduction in lnRHI values, corresponding to the increase in the number of risk factors (0.75 [0.31–1.26], 0.66 [0.25–0.97], 0.63 [0.37–1.19], 0.48 [0.32–0.71], 0.43 [0.31–0.91], respectively, for none, 1, 2, 3, and 4 cardiovascular risk factors; $P = 0.004$) (Fig. 1).

In hypertensive patients, lnRHI values did not differ significantly according various treatments. Regarding the presence of dyslipidemia, only 2 patients did not take statins or other drugs; we found no difference in lnRHI values, in comparison to patients taking any medications.

A significant positive correlation between score of adherence to Mediterranean diet and lnRHI values was found ($r = 0.307$; $P = 0.002$) (Fig. 2); according to sex differences, it was statistically significant both for men ($r = 0.370$; $P = 0.019$) and women ($r = 0.267$; $P = 0.047$). Higher adherence to Mediterranean diet was found in subjects with lnRHI values greater than 0.40 in

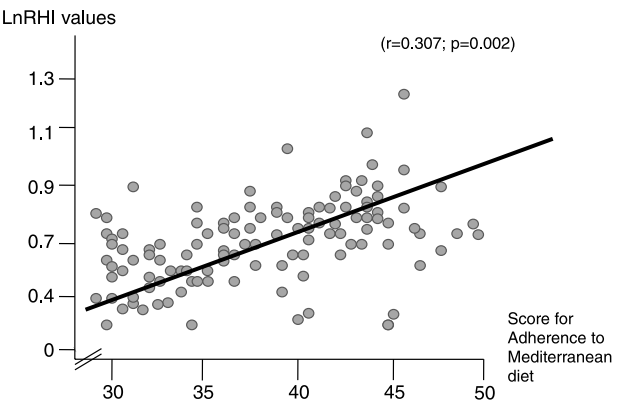


**FIGURE 2.** Correlation between score for adherence to Mediterranean diet and lnRHI values.

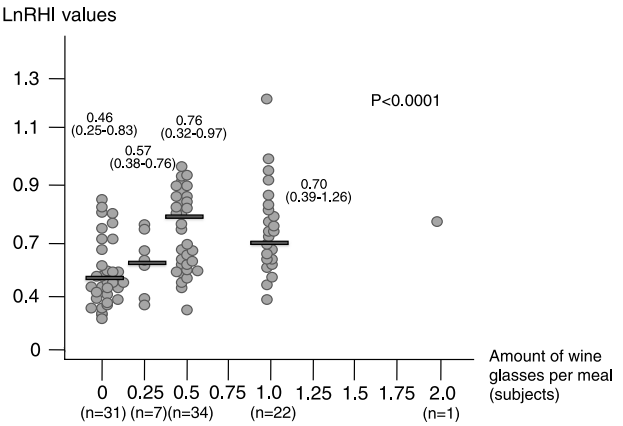


**FIGURE 3.** Correlation between red wine intake and lnRHI values. The outlier subject with high consumption was included in equal to 1 category.

comparison to others (39 [27–50] vs 33 [28–45], respectively; $P = 0.064$).

Regarding the intake of red wine, lnRHI values were significantly higher in regular drinkers in comparison to nonregular drinkers (0.46 [0.25–0.83]; 0.70 [0.32–1.26], respectively; $P < 0.0001$), and this association is confirmed for both sexes (for women: 0.47 [0.25–0.83] vs 0.76 [0.38–0.97], respectively, $P < 0.0001$; for men: 0.40 [0.31–0.54] vs 0.65 [0.32–1.26], respectively, $P = 0.005$).

We showed a significant positive relationship between red wine intake and lnRHI values (0.46 [0.25–0.83], 0.57 [0.38–0.76], 0.76 [0.32–0.97], 0.70 [0.39–1.26]; $P < 0.0001$) (Fig. 3); according to sex, lnRHI remained statistically significant for both men ($P = 0.002$) and women ($P < 0.0001$).

In our study population, different treatments were not able to influence lnRHI values. Univariate and multivariate linear regression analyses are reported in Table 3. Relationship between lnRHI and red wine consumption remained statistically significant even after adjustment for age, sex, BMI, smoking habit, hypertension, and adherence to Mediterranean diet (Table 3).

## DISCUSSION

The endothelial function assessment represents a useful approach for risk stratification of subjects and patients, and different tests have been proposed for investigating endothelial integrity. The response to ischemia by measuring arterial dilation ability is considered a good tool for exploring endothelial function, and it has been evaluated by measuring FMD as postischemia diameter increase in the arm arteries. This method has been extensively applied in vascular investigations, both clinical and experimental.

In the present study, we show the ability of PAT to pick out differences of endothelial function in relation to Mediterranean diet score and in particular to red wine consumption.

Several studies demonstrated that endothelial function evaluated by PAT is a marker providing high degrees of sensitivity and specificity when compared with the angiographic assessment of coronary artery endothelial function.[16,17] Hamburg et al.[18] provided evidence of a significant inverse relation between PAT values and multiple cardiovascular risk factors.

Furthermore, Rubinshtein et al.[19] assessed the incremental value of the PAT to the Framingham Risk Score, showing that endothelial dysfunction was an independent risk factor for future adverse cardiovascular events on multivariate linear regression analysis.

Recently, Gargiulo et al.[10] provided a substantial contribution to clarify the role of endothelial dysfunction, assessed by PAT, in systemic atherosclerotic progression; Gupta et al.[20] suggested that endothelial dysfunction may reflect cardiometabolic changes in obese prediabetic patients, representing useful tool for early cardiovascular risk assessment. Moreover, in a group of patients at high risk for vascular events as patients undergo renal transplantation, we found that PAT correlates with endothelial progenitor cells and parathyroid hormone values.[21]

The favorable effects of close adherence to Mediterranean diet in improving endothelial function were demonstrated by using FMD methodology. Rallidis et al.[11] showed an increase in FMD in 90 subjects with abdominal obesity, but without

**TABLE 3.** Univariate and Multivariate Linear Regression Analysis

| Variable | β | SE | *P* |
|---|---|---|---|
| Univariate linear regression analysis | | | |
| Red wine consumption | 0.44 | ±0.084 | **<0.0001** |
| Score of adherence to Mediterranean diet | 0.305 | ±0.007 | **0.003** |
| Sex | 0.026 | ±0.089 | 0.8 |
| Age | −0.021 | ±0.003 | 0.8 |
| BMI | −0.220 | ±0.091 | **0.037** |
| Smoking habit | −0.230 | ±0.098 | **0.021** |
| Hypertension | −0.130 | ±0.08 | **0.020** |
| Dyslipidemia | −0.055 | ±0.095 | 0.6 |
| Multivariate linear regression analysis | | | |
| Red wine consumption | 0.494 | ±0.089 | **<0.0001** |
| Score of adherence to Mediterranean diet | −0.186 | ±0.086 | 0.053 |
| Sex | −0.082 | ±0.087 | 0.4 |
| Age | 0.135 | ±0.003 | 0.2 |
| BMI | −0.025 | ±0.088 | 0.8 |
| Smoking habit | −0.182 | ±0.096 | 0.065 |
| Hypertension | −0.278 | ±0.091 | **0.009** |

cardiovascular diseases or diabetes, after 2 months of close adherence to Mediterranean-style diet (2.05%; 95% confidence interval, 0.97%–3.13%). Karatzi et al.[22] provided the evidence of an improvement in the postprandial endothelial function, assessed by FMD, in healthy subjects, after acute consumption of both red wine and green olive oil, 2 main components of Mediterranean diet.

Similarly, Widmer et al.[23] showed beneficial effects of olive oil in patients with early atherosclerosis in improving endothelial function assessed by PAT.

In our study, a beneficial dietary pattern was also associated with a healthier cardiovascular risk profile; in particular, a higher adherence to Mediterranean diet was found in patients with BMI of less than 25 kg/m$^2$ (39 [28–50] vs BMI >25 kg/m$^2$: 36 [27–46]; $P = 0.019$) and in nondyslipidemic patients (40 [27–50] vs dyslipidemic: 32 [27–48]; $P = 0.002$). These findings may explain, at least in part, the pleiotropic effects of a healthy lifestyle on anthropometric and humoral parameters and, finally, on endothelial function. However, other components of Mediterranean diet, such as red wine consumption, may exert beneficial and independent effects on cardiovascular profile, as expressed in the multivariate analyses.

In conclusion, our findings strengthen the ability of PAT to evaluate alterations of endothelium response to ischemia, in relation to physiological and clinical conditions, so indicating possible usefulness for obtaining incremental information to optimize and personalize risk stratification.

The need of better identifying subjects at high risk of cardiovascular events to whom it is more fruitful to address preventive strategies is, nowadays, diffusely perceived, so new tools for in vivo investigations have to be precisely assessed and considered for their application in clinical practice.

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