Hyperinsulinemia Is Associated With Ventricular Premature Complexes

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The study investigated a possible association between fasting plasma insulin (FPI) levels and ventricular premature complexes (VPCs). One hundred eighty-six subjects without coronary artery disease (CAD), diabetes, hypertension, and left ventricular hypertrophy were recruited. All subjects underwent 24-hour electrocardiographic monitoring and oral glucose tolerance testing. The subjects were slightly overweight, normotensive, and nondiabetic. Subjects at the third tertile of FPI concentrations were the oldest and heaviest, with prevalent upper-body fat distribution, and had enhanced fasting plasma triglyceride and potassium concentrations, lower fasting plasma high-density lipoprotein (HDL) cholesterol concentration, and a greater number of VPCs versus subjects at the first and second tertiles. Independently of age, sex, body mass index (BMI), and waist to hip ratio (WHR), VPCs were correlated with FPI concentration ($r = .19$, $P < .01$). Multiple logistic regression analyses in which the presence or absence of VPCs was the dependent variable demonstrated that FPI concentrations were associated with VPCs independently of age, sex, BMI, WHR, daily physical activity (DPA), left ventricular mass index (LVMI), plasma low-density lipoprotein (LDL)/HDL cholesterol ratio, and triglyceride concentration (odds ratio [OR], 1.2; 95% confidence interval [CI], 1.0 to 1.6). After addition to the model of fasting plasma free fatty acids ([FFA] OR, 0.7; 95% CI, 0.6 to 1.3) or potassium (OR, 0.7; 95% CI, 0.6 to 1.1) concentrations, the association between FPI concentrations and VPCs is no longer significant. In conclusion, FPI concentrations are associated with VPCs in nondiabetic, normotensive, nonischemic subjects.
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THE INSULIN RESISTANCE syndrome consists of a cluster of metabolic, anthropometric, and cardiovascular findings having as common pathophysiologic determinants insulin resistance and hyperinsulinemia.[1-3] Several studies have outlined the relationship between fasting plasma insulin (FPI) concentrations and cardiovascular activities. Deeply investigated is the link between FPI concentrations and arterial blood pressure. At least four different effects of insulin have been proposed: (1) direct activation of the sympathetic nervous system,[4] (2) insulin-stimulated changes in vascular smooth muscle cell growth,[5] (3) enhanced sodium and water retention by kidney,[6] and (4) activation of the Na/H antiporter leading to intracellular alkalinization and accumulation of intracellular Na and Ca.[7] In contrast, the effect of insulin at the myocardial level is still a matter of debate. One cannot exclude that deficient insulin action at the myocardial level might be associated with arrhythmias. In fact, it has been demonstrated that insulin stimulates myocardial hypertrophy,[2] a well-known cause of ventricular arrhythmias.[8] Nevertheless, elevated fasting plasma free fatty acids (FFA) and potassium concentrations, hallmarks of insulin resistance,[1-3] might play a further role. Since complex ventricular arrhythmia is a powerful risk factor for cardiovascular morbidity and mortality,[8] it could be of interest to investigate the association between FPI and ventricular arrhythmias.

This study investigated a possible association between FPI concentration and arrhythmias (as ventricular premature complexes [VPCs]) in nondiabetic, normotensive, nonischemic subjects.

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SUBJECTS AND METHODS

Subjects

One hundred eighty-six inpatients who came to our observation from 1992 to 1994 were selected. All patients presented for treatment of minor diseases not affecting the cardiovascular system and glucose metabolism. Subjects were excluded from the study for any of the following reasons: (1) use of drugs known to affect glucose homeostasis and arterial blood pressure; (2) use of antiarrhythmic medications; (3) presence of atrial fibrillation; (4) age less than 18 years; (5) presence of coronary artery disease (CAD), hypertension, congestive heart failure, mitral stenosis, mitral valve prolapse, and left ventricular hypertrophy; (6) presence of obesity or insulin-dependent (type I) or non–insulin-dependent (type II) diabetes mellitus; (7) family history of obesity, diabetes mellitus, and CAD; and (8) missing data regarding medication use, smoking habit, or daily physical activity (DPA). This latter parameter was evaluated according to the method used by Haskel.[9] Coffee and/or alcohol consumption was prohibited for 7 days before the study. In all subjects, cardiovascular and metabolic determinations were made. Each patient gave informed consent to participate in the study.

Cardiovascular Determinations

Blood pressure was measured on 3 different days using a standard mercury sphygmomanometer (with diastolic blood pressure corresponding to Korotkoff phase V). All determinations were made with the subject at rest after 15 minutes in the supine position, on three occasions separated by intervals of 5 minutes; the mean value of three measurements for each day was then calculated. A two-channel Holter tape recorder (Spacelab 90208, Redmond, WA) for 24-hour ambulatory electrocardiographic recordings was used. After skin preparation, the electrodes were placed on the chest to obtain the bipolar chest leads CM1 (modified V1) on the first channel and CM5 (modified V5) on the second channel. Tape recordings were analyzed by a Spacelab FT 200 Holter device. Premature depolarizations (Fig 1) and arrhythmias were identified and interpreted by a cardiologist unaware of the metabolic findings. Classification of ventricular arrhythmias was made using a method similar to that of Lown and Wolf,[10] and was based on the presence of the following arrhythmias: (1) isolated VPCs (n = 45), (2) multiform VPCs or frequent VPCs (> 30 beats/60 min, n = 15), (3) ventricular couplets (n = 33), and

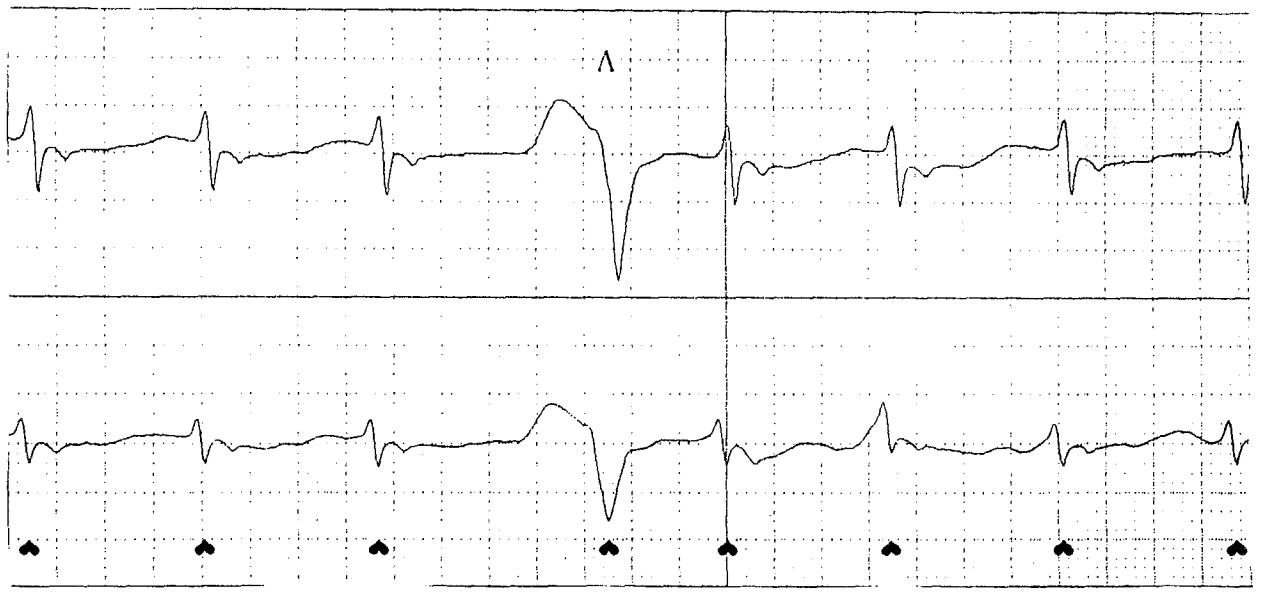

Fig 1. Electrocardiogram with a VPC. Tracings from the bipolar chest leads CM1 (modified V1) on the first channel (top) and CM5 (modified V5) on the second channel (bottom) are shown.

(4) ventricular tachycardia ($\geq$3 consecutive VPCs, n = 13). The presence of left ventricular hypertrophy was assessed by two-dimensional controlled M-mode echocardiographic recordings (Interspec-Atl Apogee CX 200, New York, NY). Measurements were obtained according to the method used by Devereux and Reicheck.[11] Left ventricular hypertrophy was characterized as a left ventricular mass to height ratio 2 SD or greater above the mean for a healthy reference population. Cutoff values for left ventricular hypertrophy were 138 g/m in men and 95 g/m in women.[12] Echocardiographic determination preceded and was made on the same day as the 24-hour electrocardiogram. To exclude the presence of CAD, all patients underwent a symptoms-limited treadmill exercise test and myocardial perfusion study with thallium 201. The exercise test was performed according to a standard Bruce protocol[13] with a Burdick treadmill (ExTol 700; Kone Instruments, Milton, WI). In all subjects, the exercise test was interrupted when the subjects reached the end of the Bruce protocol or the double product; 78% of subjects (n = 153) reached the end of the Bruce protocol. In the myocardial perfusion study, the increase in blood pressure and heart rate was within the normal range for the age of the subjects studied.

Metabolic Determinations

After an overnight fast ($\geq$12 hours), blood samples were drawn to determine plasma metabolite concentrations, and an oral glucose tolerance test (75 g glucose) was performed. Metabolic and cardiovascular studies were performed on different days.

Analytical Determinations

Plasma glucose concentrations were determined by the glucose-oxidase method on an autoanalyzer (Beckman, Fullerton, CA). Plasma fasting total and high-density lipoprotein (HDL) cholesterol, triglyceride, and potassium concentrations were determined by routine laboratory methods. Plasma FFA were determined spectrophotometrically. Plasma insulin concentrations were determined by radioimmunoassay (Sorin Biomedica, Milan, Italy; coefficient of variation, 3.1% $\pm$ 0.9%). Plasma fasting low-density lipoprotein (LDL) concentration was calculated by the Friedwald formula.[14]

Calculations and Statistical Analysis

Mean arterial blood pressure (MABP) was calculated as diastolic plus one third of systolic blood pressure. VPCs were calculated over 24 hours and then expressed as beats per 60 minutes.

All results are the mean $\pm$ SD. Fasting plasma triglycerides and insulin concentrations were log-transformed to approximate normal distribution. Univariate analysis was made to distribute all subjects in tertiles of FPI concentrations. Correlations are Pearson product-moment correlations. Partial correlation was used to evaluate the association between two variables independently of covariate. ANOVA was used to evaluate differences among each tertile for each variable studied. When ANOVA indicated a P less than .05, a Scheffé test was also performed. Multiple logistic regression analysis was used to study the association between VPCs and all variables studied. For this latter analysis, all subjects were dichotomized as those without (VPCs = 0 beats/60 min) and with VPCs. The odds ratio (OR) and 95% confidence interval (CI) for each variable or model have been calculated. P less than .05 was chosen as the level of significance. All statistical analyses were made on an IBM computer (Portsmouth, England) with the SOLO (BMDP, Cork, Ireland) software package.

RESULTS

Clinical characteristics of the subjects are reported in Table 1. The subjects were slightly overweight, normotensive nondiabetics without laboratory findings of dyslipidemia. In the univariate analysis, subjects were divided into tertiles of FPI concentrations (Table 2). Subjects at the third tertile were the oldest and heaviest, with an upper-body fat distribution. Despite a slight trend toward an increase, resting systolic and diastolic blood pressure values were not significantly different among the groups studied. The number of VPCs increased significantly from the first to the third tertile. In this last group of subjects, the number of VPCs was significantly different versus either the first or second tertile. Fasting plasma glucose had a slight but

Table 1. Clinical Characteristics of the Subjects (N = 186)

Characteristic	Mean	Range
Age (yr)	56.8	36-75
Gender (F/M)	90/96	
BMI (kg/m²)	26.1	23-28
WHR	0.83	0.79-0.87
SBP (mm Hg)	142	125-155
DBP (mm Hg)	81	75-90
LVMI (g/m)	98	72-111
EF (%)	63	60-69
VPCs (beats/60 min)	28.4	0-123
Fasting plasma glucose (mmol/L)	5.3	4.6-6.2
2-h plasma glucose (mmol/L)	6.8	4.6-7.9
FPI (pmol/L)	98	21-189
2-h plasma insulin (pmol/L)	367	168-623
Fasting plasma LDL cholesterol (mmol/L)	3.7	2.3-5.0
Fasting plasma HDL cholesterol (mmol/L)	1.1	0.88-1.5
Fasting plasma triglycerides (mmol/L)	1.6	0.75-2.7
Fasting plasma FFA (mmol/L)	0.4	0.2-0.8
Fasting plasma K (mmol/L)	4.4	4.0-5.0
DPA (mets)	5.4	4.1-6.8

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; EF, ejection fraction; mets, metabolic equivalents system.

nonsignificant trend to increase in the tertiles studied. In contrast, 2-hour plasma glucose concentration was significantly higher in subjects in the third tertile compared with those in the other tertiles. Fasting plasma LDL cholesterol increased progressively but nonsignificantly with the increase in FPI concentrations. In contrast, fasting plasma HDL cholesterol significantly declined with the increase in FPI concentrations. Fasting plasma triglycerides and potassium concentrations were also significantly different in subjects at the third tertile compared with those at the first and second tertile of FPI concentrations. The DPA level was significantly lower in subjects at the third tertile (Table 3), whereas the number of cigarettes was equally distributed within the three tertiles (data not shown). The increases in 24-hour heart rate variability and blood pressure in the myocardial perfusion study with thallium 201 were in the normal range and were not different among the three tertiles. VPCs (beats per 60 minutes) were significantly correlated with age ($r = .14$, $P < .05$), body mass index ([BMI] $r = .24$, $P < .001$), waist to hip ratio ([WHR] $r = .20$, $P < .005$), fasting plasma triglycerides ($r = .16$, $P < .04$), FFA ($r = .54$, $P < .001$; Fig 2), insulin ($r = .61$, $P < .001$; Fig 2), plasma potassium ($r = .18$, $P < .03$; Fig 2), DPA ($r = -.21$, $P < .003$), and left ventricular mass index ([LVMI] $r = .55$, $P < .001$). Strong correlations between FPI concentrations and fasting plasma triglycerides ($r = .34$, $P < .001$) or HDL cholesterol ($r = -.31$, $P < .001$) were also found. In contrast, resting systolic blood pressure, MABP, ejection fraction, and the fasting plasma LDL/HDL cholesterol ratio were not significantly correlated with VPCs. After adjusting for age, sex, BMI, WHR, DPA, and LVMI, VPCs were still significantly correlated with FPI concentrations ($r = .15$, $P < .05$).

The association of each variable with VPCs is shown in Table 3. Age, BMI, WHR, MABP, DPA, LVMI, FPI, triglycerides, FFA, and potassium concentrations were the main variables associated with VPCs. To investigate the association between FPI concentrations and VPCs independently of each covariate, a multiple logistic regression analysis was made (Table 4). The association between FPI concentrations and VPCs was independent of age, sex, BMI, WHR, MABP, DPA, LVMI, fasting plasma LDL/HDL cholesterol ratio, and fasting plasma triglyceride concentrations. After addition to the model of FFA or fasting plasma potassium concentration, the association between FPI concentration and VPCs was no longer significant (Table 4). In this latter model, FFA (OR, 1.9; 95% CI, 1.4 to 2.9) and fasting plasma potassium (OR, 1.1; 95% CI, 1.0 to 1.4) concentrations were still significantly associated with VPCs. In the multiple logistic regression

Table 2. Baseline Characteristics (mean ± SD) According to Tertiles of FPI Concentration (N = 186)

Characteristic	Tertiles of FPI Concentration				
	1	1 *v* 2	2	2 *v* 3	3
Age (yr)	48.1 ± 0.9	$P < .01$	57.5 ± 1.1	$P < .03$	67.2 ± 1.3*
BMI (kg/m²)	24.1 ± 0.5	$P < .05$	25.8 ± 0.3	$P < .05$	27.1 ± 0.4*
WHR	0.80 ± 0.02	$P < .05$	0.82 ± 0.03	$P < .05$	0.85 ± 0.02*
SBP (mm Hg)	136 ± 2.9		141 ± 3.3		144 ± 4.1
DBP (mm Hg)	83 ± 2.1		86 ± 3.4		87 ± 4.1
LVMI (g/m)	77 ± 4.1	$P < .05$	91 ± 6.7	$P < .05$	103 ± 7.2†
EF (%)	69 ± 0.9		66 ± 0.4		65 ± 0.9
VPCs (beats/60 min)	4.1 ± 2.1	$P < .01$	24.5 ± 7.8	$P < .005$	86.5 ± 31.1*
Fasting plasma glucose (mmol/L)	5.4 ± 0.3		5.5 ± 0.3		5.7 ± 0.3
2-h plasma glucose (mmol/L)	5.9 ± 0.3		6.1 ± 0.4	$P < .05$	7.1 ± 0.2*
Fasting plasma LDL cholesterol (mmol/L)	3.3 ± 0.4		3.6 ± 0.5		4.0 ± 0.6
Fasting plasma HDL cholesterol (mmol/L)	1.3 ± 0.3		1.0 ± 0.4		0.9 ± 0.3*
Fasting plasma triglycerides (mmol/L)	1.0 ± 0.3	$P < .05$	1.4 ± 0.2	$P < .03$	1.8 ± 0.3*
Fasting plasma FFA (mmol/L)	0.15 ± 0.10	$P < .05$	0.33 ± 0.17	$P < .01$	0.62 ± 0.19†
Fasting plasma K (mmol/L)	4.0 ± 0.2	$P < .05$	4.4 ± 0.1	$P < .02$	4.9 ± 0.2*
DPA (mets)	6.3 ± 0.4		5.8 ± 0.5		4.4 ± 0.2*

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; EF, ejection fraction.
*$P < .01$, †$P < .005$: *v* first tertile.

Table 3. Multiple Logistic Regression Analysis for VPCs in 186 Subjects

Variable	OR (95% CI)	P
Age	1.2 (1.0-1.8)	.04
Sex	0.7 (0.5-1.4)	.15
BMI	1.1 (1.0-1.7)	.05
WHR	1.1 (1.0-1.8)	.05
MABP	1.3 (1.1-1.9)	.01
LVMI	2.0 (1.1-3.0)	.006
EF	1.2 (0.8-1.6)	.20
2-h plasma glucose	1.1 (0.9-1.8)	.10
FPI	3.3 (2.1-4.5)	.001
Fasting plasma LDL/HDL ratio	1.3 (0.8-1.9)	.10
Fasting plasma triglycerides	1.9 (1.5-2.6)	.007
Fasting plasma FFA	4.1 (2.3-5.3)	.001
Fasting plasma K	1.8 (1.2-2.4)	.008
DPA	0.6 (0.4-0.9)	.01

NOTE. VPCs were considered present (> 0 beats/60 min) or absent (0 beats/60 min). Each variable was considered without any adjustment.

analyses, when the fasting plasma insulin to glucose ratio was used instead of FPI concentrations, the results were unchanged. Finally, we also calculated the independent effect of FFA on the occurrence of VPCs. In a model consisting of age, sex, BMI, WHR, DPA, LVMI, and MABP, FFA concentrations were no longer associated with VPCs (OR, 1.4; 95% CI, 0.8 to 2.1).

Sex Differences

There were no significant differences in age, BMI, systolic/diastolic blood pressure, LVMI, FPI, fasting LDL, HDL, triglycerides, FFA, and potassium concentrations, or number of VPCs between men and women (data not shown). In contrast, WHR (0.81 ± 0.03 *v* 0.85 ± 0.02, $P < .001$) was lower in women than in men. Despite the difference, multiple logistic regression analyses with the presence of VPCs as the dependent variable did not provide different results when performed only in men or women (data not shown).

DISCUSSION

Our study demonstrates that in subjects without CAD, hypertension, obesity, and non–insulin-dependent diabetes mellitus, FPI concentrations are directly associated with the number of VPCs. The association is independent of age, sex, BMI, WHR, DPA, LVMI, 2-hour plasma glucose, fasting plasma LDL/HDL cholesterol ratio, and triglyceride concentrations. Since fasting hyperinsulinemia is an hallmark of insulin resistance,[1-3] one can conclude that insulin resistance is associated with an higher number of VPCs.

The role of hyperinsulinemia in the genesis of CAD[1-3] and hypertension[15-16] is widely recognized. In contrast, the relationship between insulin resistance and cardiac function has been poorly investigated. To the best of our knowledge, this is the first report of a relationship between hyperinsulinemia and arrhythmias. In our patients, insulin resistance might be due to advancing age, increase in body fatness, decline in fitness, and upper-body fat distribution.[2-3] Several pathophysiological mechanisms can underlie the association between hyperinsulinemia and VPCs. Firstly, insulin resistance is associated with an increase in plasma FFA concentrations.[1-3,17-20] It has been suggested that elevated plasma FFA levels might have a detergent effect on membranes.[18] Thus, the pro-arrhythmic effect of FFA might be due to the production of lysophospholipids, derived from the breakdown of membrane lipids, and of acylcarnitine derived from circulating FFA.[21-22] Acylcarnitine inhibits the Ca^{2+} pump of the sarcoplasmic reticulum, as well as the sarcolemmal Na/Ca exchanger and Na/K

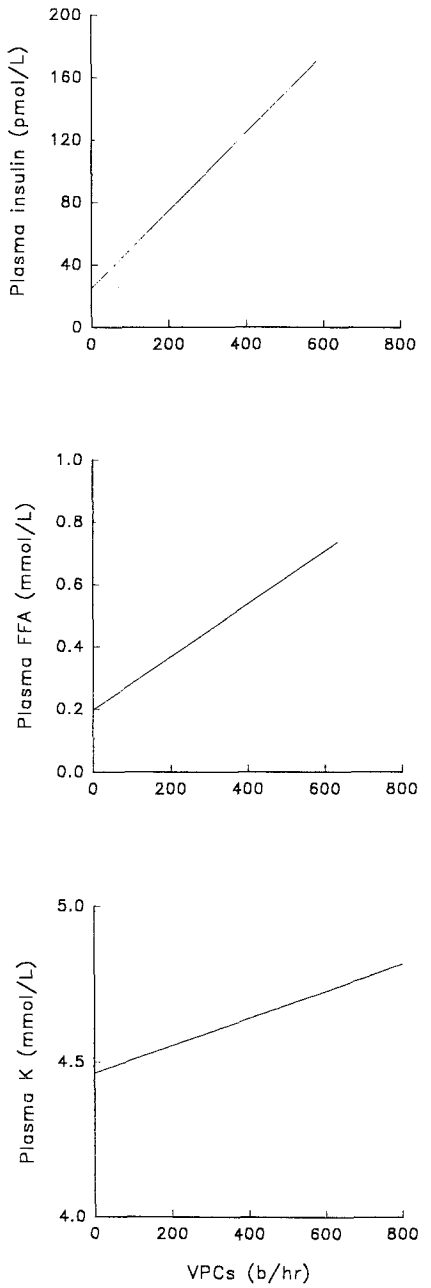

Fig 2. Simple correlations between the number (beats per hour [b/hr]) of VPCs and FPI ($r = .61$, $P < .001$), FFA ($r = .54$, $P < .001$), and potassium ($r = .18$, $P < .03$) concentrations.

Table 4. OR and 95% CI for the Association Between FPI Concentration and VPCs (N = 186)

Association of FPI Concentration With VPCs Independent of	OR	95% CI
1. Age, sex, BMI, WHR, MABP	2.0	1.1-4.2
2. Age, sex, BMI, WHR, DPA, MABP, LVMI, 2-h plasma glucose, fasting plasma LDL/HDL cholesterol ratio, fasting plasma triglycerides	1.2	1.0-1.6
3. Age, sex, BMI, WHR, DPA, MABP, LVMI, 2-h plasma glucose, fasting plasma LDL/HDL cholesterol ratio, fasting plasma triglycerides, fasting plasma FFA	0.7	0.6-1.3
4. Age, sex, BMI, WHR, DPA, MABP, LVMI, 2-h plasma glucose, fasting plasma LDL/HDL cholesterol ratio, fasting plasma triglycerides, fasting plasma K	0.7	0.6-1.1

pump.[22] These actions could promote cytosolic calcium overload, which has been linked to the development of cardiac insulin resistance[23] and to ventricular arrhythmias.[24] Furthermore, accumulation of FFA can open K-channels, a phenomenon associated with the shortening of action-potential duration.[25] Secondly, a deficient intracellular adenosine triphosphate (ATP) content could also have a role. The glycolytic pathway is the main metabolic pathway providing ATP for the integrity of myocardial plasma membranes. Insulin resistance[1-3] and the glucose–fatty acid cycle[26] may decrease glucose oxidation with a secondary decline in ATP production. Elevated plasma FFA concentrations are associated with an overdrive of the Randle cycle.[27] Myocardial cells operate with FFA as fuel,[28] and such substrate uptake is even overutilized in congestive heart failure,[29] in which insulin resistance and sympathetic nervous system overactivity are responsible for high plasma FFA concentrations.[30] Furthermore, an elevated intracellular FFA concentration might inhibit adenylnucleotide translocase with a secondary decline in ATP production within myocardial cells.[31-32] Nevertheless, the latter pathophysiological mechanism needs further confirmation.[33] A decrease in ATP concentration activates the ATP-dependent K-channels with an impoverishment of intracellular K and enhances susceptibility to the genesis of VPCs.[19,34]

A low plasma magnesium concentration might also be associated with an increased number of VPCs.[35] Unfortunately, plasma magnesium concentration was not determined in our study, so its role was not evaluated in the multiple regression analyses.

Further indirect evidence for the association between hyperinsulinemia and VPCs came from observations that in non–insulin-dependent diabetics[36] and obese patients,[37] in whom insulin resistance and elevated fasting plasma FFA concentrations[1-3] coexist, the prevalence of ventricular arrhythmias is greater than in healthy subjects.

The role of LVMI should be also evaluated. Previous studies have shown that an increase in LVMI is associated with VPCs[8] and with hyperinsulinemia/insulin resistance.[38-39] Our study showed the association between FPI and VPCs to be independent of LVMI. Such an apparent discrepancy needs to be addressed in future longitudinal studies.

In conclusion, our data provide evidence that fasting hyperinsulinemia is associated with a growing number of VPCs. Fasting plasma FFA and potassium concentrations and LVMI seem to contribute strongly to explain such an association. Future longitudinal studies should highlight the relationship between insulin resistance and the genesis of VPCs.

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