Atherosclerosis 238 (2015) 108–112

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Insulin-resistance HCV infection-related affects vascular stiffness in normotensives

Maria Perticone [a, *], Raffaele Maio [b], Eliezer Joseph Tassone [b], Giovanni Tripepi [c], Serena Di Cello [b], Sofia Miceli [b], Benedetto Caroleo [b], Angela Sciacqua [b], Anna Licata [d], Giorgio Sesti [b], Francesco Perticone [b]

[a] Department of Experimental and Clinical Medicine, University Magna Græcia of Catanzaro, Italy
[b] Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, Italy
[c] CNR-IBIM, National Research Council-Institute of Biomedicine, Clinical Epidemiology and Physiopathology of Renal Disease and Hypertension, Reggio Calabria, Italy
[d] Biomedical Department of Internal and Specialistic Medicine, University of Palermo, Italy

ARTICLE INFO

Article history:
Received 2 September 2014
Received in revised form
5 November 2014
Accepted 26 November 2014
Available online 29 November 2014

Keywords:
Insulin resistance
Chronic hepatitis C virus infection
Arterial stiffness

ABSTRACT

Background and Aims. Arterial stiffness evaluated as pulse wave velocity, is an early marker of vascular damage and an independent predictor for cardiovascular events. We investigated if the insulin resistance/hyperinsulinemia chronic hepatitis C virus infection-related could influence arterial stiffness. **Methods**. We enrolled 260 outpatients matched for age, body mass index, gender, ethnicity: 52 with never-treated uncomplicated chronic hepatitis C virus infection (HCV^+), 104 never-treated hypertensives (HT) and 104 healthy subjects (NT). Pulse wave velocity was evaluated by a validated system employing high-fidelity applanation tonometry. We also measured: fasting plasma glucose and insulin, total, LDL- and HDL-cholesterol, triglyceride, creatinine, e-GFR-EPI, HOMA, quantitative HCV-RNA. **Results**. HCV^+ patients with respect to NT had an increased pulse wave velocity (7.9 ± 2.1 vs 6.4 ± 2.1 m/s; $P < 0.0001$), similar to that observed in HT group (8.8 ± 3.2 m/s). HCV^+ patients, in comparison with NT, had higher triglyceride, creatinine, fasting insulin and HOMA (3.2 ± 1.3 vs 2.5 ± 1.0; $P < 0.0001$). At linear regression analysis, the correlation between pulse wave velocity and HOMA was similar in HT ($r = 0.380$, $P < 0.0001$) and HCV^+ ($r = 0.369$, $P = 0.004$) groups. At multiple regression analysis, HOMA resulted the major determinant of pulse wave velocity in all groups, explaining respectively 11.8%, 14.4% and 13.6% of its variation in NT, HT and HCV^+. At correlational analysis hepatitis C virus-RNA and HOMA demonstrated a strong and linear relationship between them, explaining the 72.4% of their variation ($P = 0.022$). **Conclusions**. We demonstrated a significant and direct correlation between HOMA and pulse wave velocity in HCV^+ patients, similar to that observed in hypertensives.

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1. Introduction

Abnormal arterial stiffness is associated with an increased risk for various adverse outcomes, including cardiovascular disease [1,2], stroke [2,3], and renal disease [4]. Interestingly, arterial stiffness is associated with traditional cardiovascular risk factors and metabolic alterations including obesity, impaired glucose tolerance (IGT), and dyslipidemia [5]. In addition, it reflects the structural arterial wall modifications, characterizing the vascular aging [6].

There are several evidences demonstrating that patients with chronic hepatitis C virus (HCV) infection (HCV^+) have an increased cardiovascular morbidity and mortality. In keeping with this, we recently demonstrated that HCV^+ patients have an increased left ventricular mass, similar to that of hypertensive subjects [7], mediated by hyperinsulinemia/insulin-resistance (IR) status and independently of other confounding factors [8]. These evidences have a biological plausibility because HCV^+ patients are insulin resistant as consequence of direct and indirect mechanisms, leading to both hepatic and extra-hepatic IR. In addition, the abnormal

* Corresponding author. Department of Experimental and Clinical Medicine, Campus Universitario di Germaneto, V.le Europa, 88100 Catanzaro, Italy.
E-mail address: mariaperticone@hotmail.com (M. Perticone).

http://dx.doi.org/10.1016/j.atherosclerosis.2014.11.025
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insulin signal, associated with HCV infection, is due to an interaction with the renin–angiotensin–aldosterone system [9–11].

However, all these mechanisms do not fully justify the higher cardiovascular risk of these patients. Taken together, the aim of this study was to evaluate the possible association between HCV^+ infection and abnormal arterial stiffness in comparison with a group of hypertensive patients and a group of normotensive health subjects.

2. Methods

2.1. Study population

To test our hypothesis we designed a case–control study involving patients evaluated at the University Hospital of Catanzaro. We recruited 52 HCV^+ normotensive Caucasian outpatients (40 males and 12 females, mean age 48.73 + 10.4 years). They were matched for age, body mass index and gender in a 1:2:2 ratio with 208 subjects participating to the CAtanzaro MEtabolic RIsk factors Study (CATAMERIS), 104 never treated hypertensives (HT) (77 males and 27 females, mean age 48.5 + 9.7 years) and 104 normotensives (NT) (79 males and 25 females, mean age 48.8 + 11.2 years). At the time of the first evaluation, both HCV^+ and HT patients were untreated with antiviral therapy or antihypertensive drugs. Secondary forms of hypertension were excluded by systematic testing by a standard clinical protocol including renal ultrasound studies, computed tomography, renal scan, catecholamine, plasma renin activity and aldosterone measurements. Other exclusion criteria were type-2 diabetes mellitus (T2DM) detected by an oral glucose tolerance test, according to ADA guidelines; history or clinical evidence of angina, myocardial infarction, valvular heart disease, cardiomyopathy, heart failure or peripheral vascular disease; administration of any drugs interfering with glucose metabolism; kidney, thyroid, endocrine and advanced liver diseases, transplanted patients, history of malignant disease. We collected measurements of height and weight according to a standardized protocol, and body mass index was calculated as kilograms per square meter. The Ethical Committee approved the protocol and informed written consent was obtained from all participants. All the investigations were performed in accordance with the principles of the Declaration of Helsinki.

2.2. Blood pressure measurements

Readings of clinic blood pressure (BP) were obtained in the left arm of the supine patients, after 5 min of quiet rest, with a mercury sphygmomanometer. Minimum three BP readings were taken on three separate occasions at least 2 weeks apart. Systolic and diastolic BP was recorded at the first appearance (phase I) and the disappearance (phase V) of Korotkoff sounds. Baseline BP values were the average of the last two of the three consecutive measurements obtained at intervals of 5 min. Patients with a clinic systolic BP (SBP) > 140 mmHg and/or diastolic BP (DBP) > 90 mmHg were defined as hypertensive.

2.3. Laboratory determinations

All laboratory measurements were performed after 12 h of fasting. Plasma glucose was determined immediately by the glucose oxidation method [Glucose analyzer, Beckman Coulter, Milan; intra-assay coefficient of variation (CV) 2.2%, inter-assay CV 3.8%]. Serum insulin was determined in duplicate by a highly specific radioimmunoassay using two monoclonal antibodies; intra-assay CV 2.1%, inter-assay CV 2.9%. IR was estimated by homeostasis model assessment (HOMAIR) according to the following equation: HOMA = [insulin (μU/ml) * glucose (mmol/l)]/22.5 [12]. Total, low-density lipoprotein – (LDL), and high-density lipoprotein – (HDL) cholesterol and triglyceride concentrations were measured by enzymatic methods (Roche Diagnostics GmbH, Mannheim, Germany). Creatinine was measured by using Jaffe methodology. Values of estimated glomerular filtration rate (mL/min/1.73 m^2) were calculated by using the equation proposed by investigators in the chronic kidney disease epidemiology (CKD-EPI) collaboration [13]. Quantitative HCV-RNA was assayed by a real-time polymerase chain reaction (PCR) assay.

2.4. Arterial wave reflection and central BP measurements

These measurements were obtained by a validated system (Sphygmocor™; AtCor Medical, Sydney, Australia) that employs high-fidelity applanation tonometry (Millar) and appropriate computer software for the analysis of pressure wave (Sphygmocor™). Pressure calibration was obtained through automatically, non-invasively recorded supine brachial artery BP of the dominant arm after a 30-min rest (Dinamap Compact T; Johnson & Johnson Medical Ltd, Newport, UK). BP was measured five times over 10 min and the mean of the last three measurements were taken for calibration. Pressure wave recording was performed at the radial artery of the dominant arm with the wrist softly hyperextended, and it is the average of single pressure waves recorded consecutively for eight seconds. Pressure wave recordings were accepted only if variation of peak and bottom pressures of single pressure waves was <5%. The central pressure wave was automatically derived from the radial pressures by a built-in generalized transfer function. In addition, was also obtained pressure wave measurement at the right carotid artery, as it is well known that central AI may be more accurately derived from this vascular site [14]. Central waveforms were further analyzed to identify the time to peak/shoulder of the first (T1) and second (T2) pressure wave components during systole. The pressure at the peak/shoulder of T1 was identified as outgoing pressure wave height (P1), the pressure at the peak/shoulder of T2 was identified as the reflected pressure wave height (P2), either absolutely or as percent of ejection duration. Augmentation pressure (AP) was defined as difference between P2–P1, and augmentation index (AI) as [AP/pulse pressure (PP)] *100. Aortic pulse wave velocity (PWV) was determined from carotid and femoral pressure waveforms. Carotid to femoral transit time (ΔT) was computed from the foot-to-foot time difference between carotid and femoral waveforms. The distance between the surface markings of the sternal notch and femoral artery was used to estimate the path length between the carotid and femoral arteries (L), and PWV computed as L/ΔT.

2.5. Statistical analysis

ANOVA for continuous clinical and biological data was performed to test the differences among groups, and the Bonferroni post-hoc test for multiple comparisons was further performed; for dichotomic variables we used the χ^2 test. Data are expressed as mean ± SD, and binary data as percent frequency. Correlation coefficients were calculated according to Pearson's method. The independent relationship between PWV and HOMA was investigated by univariate and multiple linear regression analysis, in the whole study population and in the three groups separately. In the multivariate model we inserted only HOMA to avoid a possible colinearity with fasting glucose and insulin. To infer the involvement of insulin sensitivity (assessed by HOMA) in the pathophysiological pathway by which hypertension and HCV lead to increased PWV in our study population we applied the analytical approach proposed by Kraemer et al. [15]. We first estimated the crude (model 1) and

adjusted (model 2) relationships between hypertension/HCV with PWV (by unadjusted and adjusted multiple linear regression analysis). In model 2 we included a series of potential confounders (BP, LDL and HDL cholesterol) but HOMA (i.e. the potential mediator of the effect of hypertension/HCV on PWV). To unravel the potential role of insulin sensitivity in the pathway linking hypertension/HCV and arterial rigidity, we introduced HOMA index in model 3 and we calculated the percent change in the beta value for the links between hypertension/HCV and PWV. The percentage reduction in the beta values is an index of the total amount of covariance between hypertension/HCV and PWV that is explained by insulin resistance. Data are expressed in terms of standardized regression coefficients (β) and *P* values. Differences were assumed to be significant at $P < 0.05$. All calculations were done with a standard statistical package (SPSS for Windows version 16.0, Chicago, IL, USA).

3. Results

3.1. Study population

Study population characteristics are reported in Table 1. Among three groups there were significant differences for central SBP (c-SBP), central DBP (c-DBP) and central pulse pressure (c-PP). In particular, as expected, these parameters were significantly higher in HT group in comparison with both NT and HCV^+ subjects, without any significant difference between these two groups. Clinically relevant, PWV, AP and AI. In particular, all these central hemodynamic parameters progressively increase from NT, to HCV^+ and HT patients. Interestingly, HCV^+ patients, respect to healthy normotensive subjects, had an increased PWV (7.9 ± 2.1 vs 6.4 ± 2.1 m/s; $P < 0.0001$), similar to that observed in HT group (8.8 ± 3.2 m/s). In addition, regarding biochemical variables, HCV^+ patients, in comparison with NT healthy subjects, had higher triglyceride, creatinine, fasting insulin and HOMA. Of interest, no differences were found in HOMA values between HT and HCV^+ (3.2 ± 1.3 vs 3.3 ± 1.3; $P = 0.651$) patients. Similarly, in HCV^+ group there was a significant higher prevalence of smokers. The mean value of HCV-RNA was 3868 ± 2963 × 10^3 (UI/ml) in HCV^+.

Table 1
Demographic, clinical, humoral and echocardiographic data of the study population and of the three groups separately.

	All ($n = 260$)	NT ($n = 104$)	HCV^+ ($n = 52$)	HT ($n = 104$)	*P* value
Age, *years*	48.6 ± 10.4	48.8 ± 11.1	48.7 ± 10.4	48.5 ± 9.7	0.972
Sex, *M/F*	196/64	79/25	40/12	77/27	0.883**
BMI, *Kg/m²*	27.8 ± 4.5	28.0 ± 5.5	27.4 ± 2.6	27.8 ± 4.3	0.742
WC, *cm*	95.8 ± 8.3	95.0 ± 9.4	96.0 ± 5.3	95.34 ± 8.4	0.347
Current smokers, *n (%)*	73 (28)	15 (14)	29 (56)	29 (28)	<0.0001**
Systolic BP, *mmHg*	134 ± 15	126 ± 12	124 ± 8§	147 ± 9*	<0.0001
Diastolic BP, *mmHg*	81 ± 10	77 ± 8	74 ± 7#§	90 ± 6*	<0.0001
PP, *mmHg*	52 ± 11	49 ± 10	50 ± 8§	57 ± 11*	<0.0001
Heart rate, *bpm*	68 ± 9	69 ± 10	66 ± 7	69 ± 8	0.086
c-SBP, *mmHg*	116 ± 17	108 ± 14	109 ± 13	128 ± 14	<0.0001
c-DBP, *mmHg*	68 ± 13	64 ± 11	66 ± 8	73 ± 15	<0.0001
c-PP, *mmHg*	48 ± 18	44 ± 17	43 ± 13	55 ± 19	<0.0001
PWV, *m/s*	7.7 ± 2.8	6.4 ± 2.1	7.9 ± 2.1	8.8 ± 3.2	<0.0001
AI, *%*	18.9 ± 11.1	16.1 ± 12.0	20.2 ± 7.9	21.2 ± 10.9	0.002
AP, *mmHg*	10 ± 7	8 ± 7	9 ± 5	13 ± 8	<0.0001
Total cholesterol, *mmol/l*	4.91 ± 0.83	4.83 ± 0.78	187 ± 33	195 ± 31	0.206
LDL-cholesterol, *mmol/l*	3.15 ± 0.83	2.97 ± 0.75	3.05 ± 0.90§	3.39 ± 0.80*	<0.0001
HDL-cholesterol, *mmol/l*	1.14 ± 0.26	1.27 ± 0.26	1.03 ± 0.21#	1.03 ± 0.23*	0.466
Triglyceride, *mmol/l*	1.37 ± 0.41	1.30 ± 0.43	1.61 ± 0.34#§	1.30 ± 0.37	<0.0001
Creatinine, *μmol/l*	63.4 ± 8.8	63.4 ± 8.8	71.3 ± 8.8#§	66.9 ± 8.8	<0.0001
e-GFR, *ml/min/ 1.73 m²*	106 ± 11	107 ± 11	103 ± 10	105 ± 12	0.101
Fasting glucose, *mmol/l*	5.17 ± 0.56	5.11 ± 0.56	5.22 ± 0.61	5.11 ± 0.61	0.479
Fasting insulin, *U/ml*	13.1 ± 5.4	11.2 ± 4.5	14.1 ± 5.5#	14.5 ± 5.6*	<0.0001
HOMA	3.0 ± 1.3	2.5 ± 1.0	3.2 ± 1.3#	3.3 ± 1.3*	<0.0001

* = $P < 0.05$ by Bonferroni HT vs NT; # = $P < 0.05$ by Bonferroni HCV^+ vs NT; § = $P < 0.05$ by Bonferroni HCV^+ vs HT; ** tested by chi-square test.

3.2. Correlational analysis

A linear regression analysis was performed to test the relationship between PWV and different covariates in the whole study population and in the three groups separately (Table 2).

In the whole study population, PWV was significantly correlated with SBP ($r = 0.331$; $P = 0.0001$), DBP ($r = 0.146$; $P = 0.009$), PP ($r = 0.306$; $P = 0.0001$), c-SBP ($r = 0.222$; $P = 0.0001$), c-PP ($r = 0.222$; $P = 0.0001$), glycemia ($r = 0.171$; $P = 0.003$), fasting insulin ($r = 0.425$; $P = 0.003$), HOMA ($r = 0.425$; $P = 0.001$), and inversely correlated with HDL-cholesterol ($r = -0.175$; $P = 0.002$).

In HT group, a linear relationship was observed between PWV and fasting insulin ($r = 0.316$; $P = 0.001$) and HOMA ($r = 0.380$; $P = 0.0001$). In addition, in this group, the other covariates significantly correlated with PWV were SBP ($r = 0.299$; $P = 0.001$), PP ($r = 0.321$; $P = 0.0001$), c-PP ($r = 0.259$; $P = 0.004$), and glycemia ($r = 0.285$; $P = 0.002$).

In HCV^+ group, PWV resulted statistically correlated with fasting insulin ($r = 0.402$; $P = 0.002$) and HOMA ($r = 0.369$; $P = 0.004$).

Table 2
Linear regression analysis between PWV and different covariates in the whole population and in the three groups.

	All (*n.* 260)	NT (*n.* 104)	HT (*n.* 104)	HCV^+ (*n.* 52)
	r/P	r/P	r/P	r/P
Age, *yrs*	0.25/0.345	−0.172/0.041	0.088/0.187	0.305/0.014
Gender, *M/F*	−0.017/0.391	−0.76/0.221	0.036/0.359	−0.135/0.170
BMI, *kg/m²*	0.001/0.497	0.073/0.231	−0.048/0.315	0.037/0.396
SBP, *mmHg*	0.331/0.0001	0.023/0.408	0.299/0.001	0.220/0.059
DBP, *mmHg*	0.146/0.009	−0.093/0.174	−0.174/0.039	0.154/0.138
PP, *mmHg*	0.306/0.0001	0.095/0.168	0.321/0.0001	0.088/0.267
c-SBP, *mmHg*	0.222/0.0001	−0.014/0.444	0.095/0.169	0.073/0.303
c-DBP, *mmHg*	−0.028/0.328	0.033/0.371	−0.253/0.005	−0.049/0.365
c-PP, *mmHg*	0.222/0.0001	−0.033/0.371	0.259/0.004	0.107/0.224
Cholesterol, *mmol/l*	0.065/0.148	−0.097/0.162	0.076/0.223	0.135/0.170
LDL-cholesterol, *mmol/l*	0.104/0.047	−0.064/0.261	0.039/0.345	0.153/0.139
HDL-cholesterol, *mmol/l*	−0.175/0.002	−0.107/0.139	0.032/0.372	−0.101/0.237
Triglyceride, *mmol/l*	0.066/0.144	−0.009/0.463	0.128/0.098	0.006/0.482
Creatinine, *μmol/l*	0.053/0.199	−0.013/0.446	−0.017/0.430	0.096/0.250
CKD-Epi, *ml/min/ 1.73 m²*	0.039/0.267	0.173/0.039	0.116/0.121	−0.304/0.434
Glycemia, *mmol/l*	0.171/0.003	0.110/0.132	0.285/0.002	−0.024/0.434
Fasting insulin, *mU/l*	0.425/0.003	0.314/0.001	0.316/0.001	0.402/0.002
HOMA	0.425/0.001	0.344/0.0001	0.380/0.0001	0.369/0.004

3.3. Multivariate analysis

A stepwise multivariate linear regression model was performed to evaluate the independent predictors of PWV in all population and in the three groups separately (Table 3). In this analysis we included as independent covariates also the gender and the smoking in addition to those resulted significant in the linear regression. In the whole population, as well as in HT and HCV$^+$ groups, HOMA was the major predictor of PWV, explaining 18.0%, 14.4% and 13.6% of its variation, respectively. In the whole population, other independent predictors were SBP and DBP, explaining respectively another 7.3% and 1.3% of PWV variation; in HT group, SBP adds another 6.5% in the PWV variation, while in HCV$^+$ group e-GFR resulted another independent predictor, explaining an additional 8.2% of its variation.

To test the hypothesis that HOMA is a mediator of the link between hypertensive/HCV status and PWV we constructed multivariate linear regression models of increasing complexity of data adjustment (Table 4). In model 1, both hypertensive (beta = 0.396, $P < 0.001$) and HCV status (beta = 0.218, $P = 0.001$) were strongly and significantly related to PWV. The strength of the hypertensive status-PWV link was critically dependent on potential confounders (namely: systolic and diastolic BPs, LDL and HDL cholesterol) because data adjustment for these covariates (model 2) reduces by 22% the strength of this association. Of note, the HCV status-PWV link was only slightly affected by data adjustment for the same set of confounders (model 2, −7.3%) suggesting that such a link is largely unexplained by these risk factors. Notably, data adjustment for HOMA (**model 3**) further reduces the strength of the associations between hypertensive status and PWV (−26%) and even more the relationship between HCV status and the same outcome variable (−29%) indicating that about 1/3 of the relationship between hypertension and HCV status with PWV is mediated by insulin resistance. Of interest, in none of the models, smoking was retained as independent predictor of vascular damage.

4. Discussion

The results of this study demonstrate, for the first time, that HCV$^+$ normotensive patients, in comparison with healthy normotensive subjects, have a significant increase of arterial stiffness assessed by PWV, an important surrogate end-point for cardiovascular morbidity and mortality [1–5]. In fact, HCV$^+$ group presents higher values of PWV than that found in NT group, similarly to that observed in hypertensive patients. These findings have clinical relevance because contribute to expand previous knowledge about the pathogenetic mechanisms underlying the high prevalence of cardiovascular morbidity and mortality in this setting of patients. In fact, there are consolidated evidences demonstrating that abnormal arterial stiffness, reflecting the arterial wall modifications, is a powerful and independent predictor for various adverse cardiovascular outcomes [1–5].

Vascular stiffness, that represents an intermediate step of vascular aging, is due to the prolonged exposure to traditional and non-traditional cardiovascular risk factors, such as IR/hyperinsulinemia [6]. The biological plausibility of this finding is also supported by present results demonstrating that, in the multiple regression analysis HOMA was retained as the first and independent predictor of PWV in the whole population, as well as in HT and HCV$^+$ groups, explaining 18.0%, 14.4% and 13.6% of its variation, respectively. Of clinical relevance, the significant association documented in HCV$^+$ patients between HOMA/hyperinsulinemia and PWV confirms previously published data demonstrating a strict relationship between HCV$^+$ infection and the development of IR, through a direct interaction between viral products and insulin signaling pathway via IRS-1-PI3-kinase-Akt [16–18]. Clinically relevant, these data are not influenced by the smoking because it was not retained as independent predictor of vascular damage neither in the whole population nor in the HCV$^+$ group.

An additional finding of this study is that in HCV$^+$ patients an additional independent predictor of PWV is the estimated glomerular filtration rate, another independent predictor of vascular damage [19,20] and cardiovascular events [21,22]. This is not surprising because we have previously demonstrated that IR/hyperinsulinemia, associated with a reduction in circulating levels of insulin growth factor-1, impairs the renal function through changes in renal blood flow and renal vascular resistance [23]. All these conditions interact between them in a multiplicative manner amplifying the progression of vascular damage that represents an early step in the pathophysiology of atherosclerotic disease. In keeping with this, our data contribute to explain one of the possible pathogenetic mechanism linking the HCV infection to atherosclerosis [24,25].

Of clinical relevance, at this mechanism also participate the increase of the aortic hemodynamic parameters, such as AI that reflects the degree of aortic compliance. In fact, the aorta buffering the pulsatile energy generated by the heart at each cardiac cycles, decreases both the afterload and stroke work [1,5]. In this way, it operates in reducing cardiac work and preventing the cardiac hypertrophy and modulating nitric oxide bioavailability that exerts several protective effects on vascular wall. In keeping with this, we

Table 3
Multivariate analysis of PWV in whole population and in the three groups.

	r^2 partial	r^2 total	*P*
All			
HOMA	18.0	18.0	<0.0001
SBP, *mmHg*	7.3	25.3	<0.0001
DBP, *mmHg*	1.3	26.6	0.036
NT			
HOMA	11.8	11.8	0.001
HT			
HOMA	14.4	14.4	<0.0001
SBP, *mmHg*	6.5	20.9	0.005
HCV$^+$			
HOMA	13.6	13.6	0.007
e-GFR, *ml/min/1.73 m^2*	8.2	21.8	0.028

HOMA = homeostasis model assessment; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 4
Multivariate analysis of PWV at increasing complexity of data adjustment.

	Beta	[a]Reduction in beta value (%)	*P*
Model 1			
Hypertensive status (versus NT)	0.396	…	<0.0001
HCV status (versus NT)	0.218	…	0.001
Model 2			
Hypertensive status (versus NT)	0.309	−22%	0.001
HCV status (versus NT)	0.202	−7.3%	0.00
Model 3			
Hypertensive status (versus NT)	0.229	−26%	0.01
HCV status (versus NT)	0.143	−29%	0.02

Model 1 = Hypertensive status + HCV status.
Model 2 = Model 1 + systolic and diastolic BP, LDL- and HDL-cholesterol.
Model 3 = Model 2 + HOMA.
HOMA = homeostasis model assessment.
NT = normotensive healthy subjects.
[a] The reductions in beta values between the two key exposures (hypertensive and HCV status) and the dependent variable (PWV) in models of increasing complexity of data adjustment were calculated as percentage reductions in this parameter between each multivariate model from the previous one.

recently demonstrated that AI heart rate-related is significantly correlated with endothelium-dependent vasodilation; in particular, the reduction of AI is associated with an increase on nitric oxide bioavailability [26].

5. Conclusions

Chronic HCV$^+$ inflammation, through its metabolic and proinflammatory effects, interferes with the structure of arterial wall promoting atherogenesis through direct and indirect mechanisms; so, it could be regarded as a new factor for cardiovascular risk. Based on these evidences, it is desirable to better define the risk profile in HCV$^+$ subjects and therefore it is reasonable to recommend the detection of subclinical organ damage, such as vascular stiffness.

6. Study limitations

In this study we did not perform liver biopsy because the diagnosis of HCV infection has been made on the basis of clinical and laboratory data, as recommended by the Guidelines.

Financial support

None.

Conflict of interest

The authors declare no conflict of interest.

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