**BLOOD PRESSURE (BP) MEASUREMENT.**

Brachial systolic and diastolic blood pressure (BP) was measured by a trained nurse using an automated oscillometric device (Omron M6 Comfort; Omron Healthcare, Amsterdam, Netherlands) in the right arm, with participants lying in the supine position for 10 min. Three BP readings were taken at 2-min interval, and the mean was used for data analysis according to the scientific statement from the American Heart Association1.

**MEASUREMENT OF POSTISCHEMIC REACTIVE HYPEREMIA BY LASER-DOPPLER FLOWMETRY.**

A Laser-Doppler linear Periflux System 5000 (Perimed SA, Järfälla, Sweden) was used to measure flow mediated dilatation (FMD). The test was performed in the morning after 12h of fasting. The participant was taken into a quiet room at our Day Hospital with only the researcher and a nurse present. The room temperature was maintained at 22°C and the technique and possible symptoms were explained in detail. The BP cuff was placed on the patient’s arm, with the participant in the supine position and after 15 minutes resting. The laser was attached on the forearm at 15 cm from the wrist. Then, the BP cuff was inflated to 40mmHg above the systolic BP and maintained at this pressure for 4 min. During this period, the monitoring system showed how perfusion unit (PU) decrease and reach the biological zero. Afterwards, the BP was rapidly deflated and how quickly PU rise above the pre-ischemic PU values was monitored. The data were recorded and analyzed using the Perisoft for Windows. The values of hyperemic response after the ischemia (AH) and the Peak flow (PF) were automatically calculated. The same researcher to avoid variability performed all measurement.

**LIVER STIFFNESS MEASUREMENT**

Fasting patients underwent transient elastography (Fibroscan® Echosens 502 Touch with XL and M probe) on the right lobe of the liver by trained nurse at Hospital. At total of 10 valid measurements were obtained at each assessment and the median was determined. Quality of each measurement was assessed by kPa/IQR ratio. Liver stiffness values were used to estimate the METAVIR fibrosis stage as follows: F0-F1: 2.5 to 6.9 kPa; F2: 7.0 to 9.4 kPa; F3: 9.5 to 12.4 kPa; F4: ≥ 12.5 kPa. Cirrhosis was defined as liver stiffness score of 12.5kPa or more. Liver stiffness was performed at baseline and at 52 weeks after end of treatment.

**ARTERIAL BRACHIAL INDEX (ABI)**

All measurements were obtained by a trained nurse in a quiet room with comfortable temperature, after the patient had rested for 15 minutes in the supine decubitus position. The ABI was determined by an automatic method using a validated oscillometric device (microlife, Watch BP office) that allows simultaneous arm-leg BP measurements. The ABI is automatically calculated by the division of the highest SPB of the lower limbs by the highest of the brachial SBPs. Individuals with an ABI <0.90 in either leg was classiﬁed as having peripheral arterial disease (PAD) on the basis of the scientific statement from the American Heart Association1.

**QUANTIFICATION OF EMPs, PMPs.**

Fifty µL Platelet- poor plasma was incubated with a monoclonal antibody anti-CD31-FITC antibody (BD Pharmingen. BD Bioscience, CA), and anti-CD41-Pacific blue, followed by 20 min incubation with PE-conjugated Annexin V (AV) kits according to the manufacturer's instructions (BD Pharmingen, BD bioscience, CA). AV+ was used to determinate apoptotic microparticles, CD31 FITC and CD41-Pacific blue were used to differentiate between CD31+CD41+ PMPs and CD31+CD41– EMPs. The negative control (zero value) were obtained using the isotype antibodies. Flow Count Beads (Beckman Coulter, Marseille, France) were added. MPs were identified as events with a 0.1-1μm diameter on forward light scatter (FSC) and side-angle light scatter (SSC) intensity dot plot representation, by comparison to flow cytometry calibration beads (Flow count ® calibrator beads, Beckman Coulter, Marseille, France). Data represent the mean (± SEM) of two independent experiments.

**QUATIFICATION OF cfDNA**

DNA from 400 μL of serum samples was extracted with the automatized MagNaPure Compact Instrument (Roche Diagnostics, Bassel, Switzerland) by using Magna Pure Compact Nucleic Acid Isolation Kit I, according to the protocol ‘‘Total DNA Plasma 100 400 V3 1’’. DNA was eluted in a final volume of 50 μL and frozen at -20ºC. Serum DNA was measured using a quantitative PCR (qPCR) assay using a Light-Cycler 480 Real-Time PCR instrument (Roche Diagnostics, Bassel, Switzerland). qPCR analysis was performed by 5´ nuclease assay (hydrolysis probe assay). Two microliters of DNA were amplified in a final volume of 20 µl by using LC480 Probes Master Kit (Roche® Diagnostics, Bassel, Switzerland) according to the manufacturer instructions. The β-globin hydrolysis probe system consists of the primers Forward (5´-GTG CAC CTG ACT CCT GAG GAG A-3´), Reverse (5´-CCT TGA TAC CAA CCT GCC CAG-3´), and a dual-labeled fluorescent hydrolysis probe (5´-(FAM) TCT GGC CAA GTT TCA ACT CTG CTC GCT -3´ BBQ). Amplification was performed at 95ºC 5” and 62ºC 20” for 48 cycles. Final size of the amplicon was 102 bp. Data represent the mean of two independent experiments.

**Table S1: Treatment at baseline and during de follow up period of patients who achieved SVR.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Before treatment | During  Treatment | Folow up  (After SVR) |
| **Diabetes Mellitus (n=23, 21.1%)**  Insulin    Oral Antidiabetics Agent (OAA)  Insulin + OAA  Dietetic treatment | 7 (30.4)  12 (52.2)  1 (4.3)  3 (13.1) | 7 (30.4)  12 (52.2)  1 (4.3)  3 (13.1) | 7 (30.4)  12 (52.2)  1 (4.3)  3 (13.1) |
| **Hypertension (n=35; 32.1%)**  B blocker  At1 blocker  B blocker + At1 blocker  ACE- Inhibitor  ACE- Inhibitor + B blocker  Calcium antagonist  At1 blocker+ Calcium antagonist  ACE- Inhibitor + Calcium antagonist  Diuretics  Without treatment | 1 (2.8)  5 (14.3)  1 (2.8)  13 (37.2)  4 (11.4)  2 (5.7)  2 (5.7)  1 (2.8)  1 (2.8)  5 (15.6%) | 0  5 (14.3)  1 (2.8)  14 (40)  4 (11.4)  2 (5.7)  2 (5.7)  1 (2.8)  1 (2.8)  5 (15.6%) | 2 (5.7)  5 (14.3)  1 (2.8)  13 (37.2)  3 ()  3 ()  2 (5.7)  0  1 (2.8)  5 (15.6%) |
| **Dyslipemia** (n=10; 9.2)  Atorvastatin  Simvastatin  Rosuvastatin  Without treatment | 2 ()  3  1  4 () | 0  0  0  4 () | 2 ()  3  0  4 () |
| **Hypertriglyceridemia,** (n=2, 1.8)  Gemfibrozil  Without treatment | 1 (50%)  1 (50%) | 1 (50%)  1 (50%) | 1 (50%)  1 (50%) |

At1 blocker, angiotensin II type 1 receptor (AT1) blocker; ACE- Inhibitor, Angiotensin-converting-enzyme inhibitors.

**Table S2**: Lipid profile at baseline between compensated and decompensated cirrhotic patients.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Compensated (35/45)** | **Decompensated (10/45)** | **P value** |
| **TC (mg/dl)** | 149.03±6.1 | 158.1±14.7 | 0.491 |
| **cHDL (mg/dl)** | 47.7±3.1 | 54.7±10.9 | 0.481 |
| **cLDL (mg/dl)** | 84.7±6.5 | 81.8±9.7 | 0.813 |
| **TG (mg/dl)** | 98.3±8.2 | 95.2±15.4 | 0.718 |
| **ApoA(mg/dl)** | 144.7±5.7 | 138.1±8.7 | 0.533 |
| **ApoB (mg/dl)** | 79.3±5.2 | 76.2±4.9 | 0.519 |
| **Lp(a) (mg/dl)** | 7.8±2.3 | 2.3±0.6 | 0.632 |

Non-categorical variables that were normally distributed were analyzed with Student's t test. Variables that were not normally distributed were analyzed with U *Mann*-*Whitney* test. P values are from comparison of the two groups. Data are represented as mean ± SEM.

**Table S3: Biochemical data of patients without SVR (n=5).**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Baseline** | **12 weeks (SVR)** | **1 Year FU** | **P value** |
| **Carbohydrate metabolism** | | | | |
| Glucose (mg/dl) | 94[88-123.5] | 96[87.5-108] | 106[91-116] | 0.623 |
| Insulin (µu/ml) | 17.3±7.5 | 15.1±3.6 | 18.2±5.1 | 0.819 |
| HOMA index | 3.3[2.5-7.4] | 3.5[3.2-5.8] | 5.5[3.3-5.8] | 0.549 |
| HbA1c (%) | 5.9±1.2 | 6.6±2.5 | 5.4±0.9 | 0.504 |
| **Lipid metabolism** | | | | |
| TC (mg/dl) | 144.4±47.8 | 153±45.9 | 156.2±39.4 | 0.247 |
| cHDL (mg/dl) | 38±1.2 | 47±2.8 | 43±11.3 | 0.607 |
| cLDL (mg/dl) | 68±12.7 | 66.5±30.4 | 69.5±4.9 | 1.000 |
| TG (mg/dl) | 88±34.4 | 87±27.1 | 94.4±44.2 | 0.819 |
| ApoA(mg/dl) | 144.4±45.6 | 164.2±38.7 | 158.8±43.4 | 0.549 |
| ApoB (mg/dl) | 65.1±14.2 | 70±23.5 | 73±17.9 | 0.819 |
| Lp(a) (mg/dL) | 2.8±2.1 | 3±2.2 | 3.2±2.1 | 0.497 |
| **Liver disease** | | | | |
| Platelets (109/l) | 147.8±80.9 | 171.4±92.6 | 159±90.65 | 0.247 |
| MPV (fL) | 9.5[8.9-11.5] | 11.4[10.6-18.8] | 11[10.3-12] | **0.022** |
| INR | 1.10±0.1 | 1.08±0.1 | 1.1±0.1 | 0.449 |
| Bilirubin (mg/dl) | 0.94±0.6 | 0.94±0.7 | 0.93±0.9 | 1.000 |
| AST (U/L) | 43[35-96] | 40[23-57] | 70[30-112] | 0.196 |
| ALT(U/L) | 52±14 | 39±16 | 77.8±52 | 0.331 |
| GGT (U/L) | 107±96 | 64.6±51 | 64.2±49 | 0.331 |
| Creatinine (mg/dl) | 0.8±0.2 | 0.8±0.2 | 0.8±0.1 | 0.623 |
| **Cardiovascular risk** |  |  |  |  |
| usPCR (mg/l) | 0.5[0.4-3.3] | 0.5[0.4-2.8] | 0.6[0.5-0.9] | 0.846 |
| Uric Acid (mg/l) | 4.8±1.2 | 4.9±1.8 | 4.5±1.2 | 0.174 |
| Homocysteine (µm/l) | 13.2±2.01 | 15.3±2.4 | 13.9±1.8 | 0.549 |
| Pro-BNP (pg/ml) | 37.4±29 | 38.9±26.5 | 28.2±21.1 | 0.717 |

SVR, sustained virological response; FU, Follow up; Hg, hemoglobin; INR, international normalized ratio; PT, Prothrombin time; CT, total cholesterol; cHDL high density lipoprotein cholesterol; cLDL low density lipoprotein Cholesterol; TG, triglycerides; ApoA, Apolipoproteina A; ApoB, apolipoprotein B; Lp(a); lipoprotein A; MPV, mean platelet volume; NA, sodium; K, Potassium; AST, aspartate aminotransferase; ALT, Alanine Aminotransferase; GGT, Gamma-Glutamyl Transferase; Non-categorical variables were expressed by mean ± standard deviation (SD) or median and interquartile range 25th-75th.

**Table S4: Adhesion, oxidative stress and angiogenesis soluble markers and microparticles of patients without SVR (n=5).**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Baseline** | **12 weeks (SVR)** | **1 Year FU** | **P value** |
| **VCAM (ng/ml)** | 1744.7±694.1 | 2012.9±679.6 | 2057.9±591 | 0.449 |
| **E-selectin** **(ng/ml)** | 44.7±3 | 47.1±8.1 | 38±6.3 | 0.247 |
| **VEGF (pg/ml)** | 176.8±38.6 | 216.4±46.9 | 208.8±49.2 | 0.549 |
| **OLAb (u/l)** | 369.9±117.9 | 292.4±98.6 | 523.2±101.6 | 0.091 |
| **EMPs (u/µl)** | 121.6±53.4 | 277.6±161 | 224.2±169.5 | 0.819 |
| **PMPs (u/µl)** | 1289.6±610.4 | 3028.8±2364 | 555.5±388.9 | 0.074 |

Non-categorical variables that were normally distributed were analyzed with Anova test for repeated measures. Variables that were not normally distributed were analyzed with Friedman test. P values are from comparison of the three groups. SVR, sustained virological response; FU, Follow up; VCAM, Vascular Cell Adhesion Molecule; VEGF, Vascular Endothelial Growth Factor; EMPs, Endothelial apoptotic Microparticles; PMPs, Platelet microparticles. Data are represented as mean ± SEM.

**Table S5:** Changes on surrogate markers of portal hypertension (platelets count) and liver dysfunction (MELD score) in patients with liver cirrhosis after SVR.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Platelet improvement (27/41)** | **No platelet improvement (14/41)** | **P value** |
| **Δ VCAM (ng/ml)** | -945.7±204.6 | -842.3±197.5 | 0.750 |
| **Δ E-selectin (ng/ml)** | -22.8±3.1 | -30.3±5.2 | 0.184 |
| **Δ EMPs (u/µl)** | 174.7±300.9 | 53.1±107.5 | 0.734 |
| **Δ PMPs (u/µl)** | 29.9±112.2 | 2109.2±1724.8 | 0.307 |
| **Δ cfDNA (ng/ml)** | -92.2±115.5 | 86.9±210.1 | 0.429 |
| **Δ ABI** | 0.01±0.06 | 0.08±0.06 | 0.408 |
| **Δ AH (PU)** | -224.5±255.7 | 240.9±346 | 0.289 |
|  | **MELD improvement (10/39)** | **No MELD improvement (29/39)** | **P value** |
| **Δ VCAM (ng/ml)** | -1155.6±321.4 | -763.1±173.3 | 0.277 |
| **Δ E-selectin (ng/ml)** | -24.5±8.3 | -25.89±2.8 | 0.832 |
| **Δ EMPs (u/µl)** | -71.9±119.6 | 213.3±280.9 | 0.162 |
| **Δ PMPs (u/µl)** | 2316±297.7 | 28.3±111.3 | 0.711 |
| **Δ cfDNA (ng/ml)** | 116.6±312.4 | -138.4±103.9 | 0.320 |
| **Δ ABI** | 0.12±0.1 | 0.02±0.05 | 0.376 |
| **Δ AH (PU)** | 272.5±304.6 | -86.4±263.6 | 0.476 |

Data are represented as mean ± SD. Δ represented the difference between 1-year FU and baseline. Improvement was considered if platelets increase in 15% or MELD decrease in 15% from baseline to 1-year FU. Non-categorical variables that were normally distributed were analyzed with Student's t test. Variables that were not normally distributed were analyzed with U *Mann*-*Whitney* test. P values are from comparison of the two groups. Data are represented as mean ± SEM.

**References**

1 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2017; 71:e13–e115.