Background: Patients coinfected with HIV and HCV are at risk for developing portal hypertension (PHT), hyperdynamic circulation and pulmonary arterial hypertension (PAH). Data on the influence of antiviral therapy with pegylated interferon-α (PEG-IFN-α) and ribavirin (RBV) are limited.

Methods: Haemodynamic parameters, including hepatic venous pressure gradient (HVPG), pulmonary arterial pressure (PAPmean), cardiac output (CO) and systemic vascular resistance (SysVR), were prospectively evaluated before and after PEG-IFN-α+RBV therapy in 80 HIV–HCV-coinfected patients.

Results: Baseline evaluation showed a mean HVPG of 4.7 mmHg, CO of 6.15 l/min and PAPmean of 14.8 mmHg. PHT was present in 26% of patients, hyperdynamic circulation in 5% and PAH in 4%. Patients with advanced fibrosis (METAVIR stage F3/F4; n=32) had significantly higher CO (P=0.008), lower SysVR (P=0.035), higher PAPmean (P=0.018) and higher pulmonary vascular resistance (P=0.022) than patients with stage F0–F2 fibrosis (n=48). Both hyperdynamic circulation and PAH were significantly associated with liver stiffness, fibrosis stage and portal pressure; a non-significant trend was found for CD4+ T-cell counts and HIV RNA levels. No significant changes in PAPmean, CO and SysVR were observed after PEG-IFN-α+RBV treatment, although a significant decrease in HVPG was noted in patients with HCV eradication (P=0.013).

Conclusions: The overall prevalence of hyperdynamic circulation and PAH in HIV–HCV coinfection is low. Advanced fibrosis, increased liver stiffness, elevated portal pressure and probably CD4+ T-cell count and HIV viraemia represent risk factors for hyperdynamic circulation and PAH. PHT is present in 26% of HIV–HCV-coinfected patients evaluated for antiviral therapy. Successful HCV eradication significantly decreases HVPG.

Introduction

HCV coinfection is diagnosed in about one-third of HIV patients with varying prevalence according to risk behaviour [1,2]. As HIV coinfector accelerates the natural history of HCV infection, more patients develop liver cirrhosis and complications such as portal hypertension (PHT) and hyperdynamic circulation [3,4]. HIV itself might also worsen portal, pulmonary and systemic haemodynamics by increasing intestinal permeability and bacterial translocation (endotoxaemia), causing endothelial dysfunction and leading to a pro-inflammatory state [5–7]. Because combination antiretroviral therapy (cART) has decreased mortality in HIV patients, comorbidities like HCV-related cirrhosis with portal hypertension [8] or cardiovascular diseases [9] (for example, pulmonary arterial hypertension [PAH]) have become more apparent in HIV patients. There are several conditions in which PAH can arise in HIV–HCV-coinfected patients harbouring specific risk factors for the development of distinct subtypes of PAH. Firstly, patients can suffer from porto-pulmonary hypertension (PPHTN) due to HCV-associated liver cirrhosis
[10]. Secondly, HIV–HCV-coinfected patients can develop HIV-associated pulmonary arterial hypertension (HIV-PAH) [11]. The exact mechanisms responsible for HIV-PAH are unknown, but indirect actions through secondary messengers such as cytokines [12], growth factors or endothelin 1 are strongly suspected [13,14]. This hypothesis is corroborated by the presence of perivascular inflammatory cells in HIV-PAH [15]. The prevalence of HIV-PAH in HIV-monoinfected patients was recently reported to be 0.46% [16], whereas the prevalence of PPHTN is 2–6% [17] in patients with cirrhosis and portal hypertension.

The development of hyperdynamic circulation, characterized by an increase in cardiac output, a decrease of systemic vascular resistance and cirrhotic cardiomyopathy is associated with a poor outcome in patients with liver cirrhosis [18,19]. In addition to haemodynamic alterations associated with HCV-related liver disease (for example, progressive vaso-dilation, activation of the endothelial nitric oxide synthase and the renin angiotensin aldosterone system) [20], HIV causes systemic inflammation and endothelial dysfunction by impairing the immunological and epithelial integrity of the mucosal and epithelial barrier leading to subsequent bacterial translocation and endotoxaemia [5]. Thus, systemic haemodynamic alterations can be even more pronounced in cirrhotic HIV–HCV-coinfected patients than in HCV-monoinfected patients.

Studies have shown that cART ameliorates liver disease progression [21] and decreases both bacterial translocation and the pro-inflammatory state [5,22], although data on the effects of antiviral therapy with pegylated interferon-α and ribavirin (PEG-IFN-α+RBV) on pulmonary, systemic and hepatic haemodynamics in HIV–HCV-coinfected patients are not available. As eradication of HCV decreases inflammation and endothelial dysfunction in HIV–HCV-coinfected patients [23], we hypothesized that HCV clearance not only decreases portal pressure but also improves pulmonary and systemic haemodynamic alterations.

Despite the increasing clinical relevance of PHT and HIV-PAH in HIV patients, the prevalence and severity of both diseases have not been prospectively assessed in the ‘risk group’ of HIV–HCV-coinfected patients. Thus, our study had four key aims. Firstly, we aimed to investigate the influence of advanced fibrosis on systemic and pulmonary haemodynamics. Thirdly, we investigated the effect of antiviral therapy with PEG-IFN-α+RBV on portal pressure, pulmonary and systemic haemodynamics. Finally, we evaluated the effect of HCV clearance on hepatic, pulmonary or systemic haemodynamics.

### Methods

**Patients and antiviral treatment**

All patients were included in a prospective trial at the Medical University of Vienna evaluating the safety and efficacy of antiviral therapy with PEG-IFN-α+RBV in HIV–HCV-coinfected patients (HIVCOPEG) [24]. The trial was conducted according to the principles of the Helsinki Declaration and approved by the local ethics committee. This study presents the results of the secondary end point analysis assessing hepatic, systemic and pulmonary haemodynamics in HIV–HCV-coinfected patients and the influence of antiviral therapy on haemodynamic parameters. Inclusion criteria were proven HIV infection (anti-HIV-1/2 positivity), chronic HCV infection (HCV RNA detectable for >6 months), no prior PEG-IFN-α or standard IFN-based antiviral therapy, CD4+ T-cell count >200 cells/μl (or >100 cells/μl if on cART). Exclusion criteria were hepatitis B surface antigen positivity, significant renal (serum creatinine >1.5 mg/dl), pulmonary, cardiovascular or psychiatric disease, diagnosis of hepatocellular carcinoma or other malignancy. The treatment period with PEG-IFN-α+RBV was 48 weeks irrespective of HCV genotype. Smoking habits were recorded and patients were classified as current smokers, past smokers or non-smokers. Antiretroviral drugs used for cART, including past exposure to didanosine (ddI), were recorded. All patients were treated with PEG-IFN-α2a 180 μg/week (Pegasys®, Roche, Vienna, Austria). Patients with HCV genotype 2 and 3 infections received 800 mg/day of RBV (Copegus®, Roche). Patients with HCV genotype 1/4 infection received 1,000–1,200 mg/day of RBV, which was reduced to 800 mg/day at treatment week 12. Screening investigations included liver biopsy (scored by METAVIR), transient elastography (by FibroS can®, Echosens, France) and laboratory investigations (including blood chemistry, blood cell counts, CD4+ T-cell counts, HCV genotype, HCV RNA levels and HIV RNA levels). Patients had clinical visits for screening at baseline, every 4 weeks during antiviral therapy and at follow-up visits 1, 3 and 6 months after cessation of PEG-IFN-α+RBV treatment. Haemodynamic assessments (liver vein catheterization and right heart catheterization) were performed at screening (≤4 weeks prior to baseline) and within 6 months after completion of antiviral therapy.

**Pulmonary and systemic haemodynamic measurements**

According to current guidelines [25], right heart catheterization is recommended to confirm the diagnosis of PAH. Several parameters were recorded during right heart catheterization: heart rate, right atrial pressure, pulmonary arterial pressure (PAP; systolic, diastolic and
mean), pulmonary capillary wedge pressure (PCWP),
cardiac output (CO; by thermodilution in triplicate
measures), cardiac index (CO per body surface area),
blood pressure, pulmonary vascular resistance (PuVR),
systemic vascular resistance (SysVR) and arterial and
mixed venous (pulmonary artery) oxygen saturation.
Vascular resistance defines the resistance to flow that
must be overcome to push blood through the circula-
tory system. Normal values for SysVR are 700–1,600
dyn s/cm² and for PuVR are 20–130 dyn s/cm².

Hepatic haemodynamic measurements
Portal pressure was measured by the hepatic venous
pressure gradient (HVPG) as previously described
[26,27]. Briefly, under ultrasound guidance and local
anaesthesia a catheter introducer set was placed in
the right internal jugular vein by using the Seldinger
technique. A balloon catheter (Meditech 7F, Boston,
Vienna, Austria) was introduced over the upper and
lower inferior caval vein bypassing the heart and
entering into a large liver vein. Correct placement and
sufficient wedge position were checked by X-ray. At
least three repeated measurements of free and wedged
hepatic vein pressure were performed to calculate the
HVPG. Pressure curves were continuously recorded
using an electronic interface.

Definitions of HIV-PAH, PHT and hyperdynamic
circulation
The upper limit of normal PAP mean is <20 mmHg
[25]. PAH is defined by a PAP mean ≥25 mmHg [25]. A
PCWP≤15 mmHg excluded the presence of venous
(post-capillary) pulmonary hypertension in patients
with concomitant left heart disease [25]. HIV-PAH was
diagnosed when haemodynamic criteria for PAH were
fulfilled and other causes of PAH (for example, left
heart diseases, lung diseases, chronic thromboembolic
pulmonary hypertension and collagen vascular disease)
were excluded [25].

Normal portal pressure is defined as an HVPG value
of ≤5 mmHg, whereas PHT and clinically significant
portal hypertension (CSPH) are defined as an HVPG
of 6–9 mmHg and ≥10 mmHg, respectively [28,29].
Hyperdynamic circulation is diagnosed by a cardiac
index >4.5 l/min and a SysVR <600 dyn s/cm².

Portopulmonary hypertension (PPHTN) is defined as
HVPG≥10 mmHg and a PAP mean ≥25 mmHg.

Statistical analysis
Demographic and haemodynamic data from HIV–
HCV-coinfected patients are presented as the mean
and standard deviation (sd) if not otherwise specified.
Continuous variables were compared between patients
with advanced fibrosis (META VIR score F3/4) and patients
without advanced fibrosis (META VIR score F0–F2)
using the non-parametric Mann–Whitney U test. Indi-
vidual haemodynamic parameters measured before and
after antiviral therapy were compared using paired Stu-
dent’s t-test. Categorial variables were compared using
χ² or Fisher’s exact test. P-values of <0.05 were con-
sidered to denote statistical significance. All statistical
analyses were performed using Statistica for Windows
Version 6.0 (Statsoft, Hamburg, Germany).

Results
Patient characteristics and prevalence of PHT and PAH
Patient characteristics are summarised in Table 1. Of
991 HIV patients diagnosed at the Medical University
of Vienna, 284 patients had chronic HCV coinfection.
After excluding patients with contraindications to
PEG-IFN-α+RBV or non-compliance to clinical
visits (n=123) and patients with exclusion criteria for
study entry (n=34), 127 HIV–HCV-coinfected patients
met the inclusion criteria. Of these, 80 HIV–HCV-
coinfected patients agreed to baseline evaluation of
hepatic, systemic and pulmonary haemodynamics. The
majority of patients were male (78%) with a mean
age of 38 years and a mean body mass index (BMI) of
23.3 kg/m². A total of 32 patients (40%) had advanced
fibrosis (META VIR F3/4). Mean portal pressure was
4.7 mmHg with 26% and 5% of patients presenting
with portal hypertension (HVPG≥5 mmHg) and hyper-
dynamic circulation, respectively. The mean PAP mean
of the study population was 14.8 mmHg and PAH was
diagnosed in three patients (4%), including one patient
who smoked. According to smoking habits, 41 patients
were smokers, 29 were past smokers and 10 patients
were non-smokers. No differences in baseline charac-
teristics were noted between smokers, past-smokers
and non-smokers, especially when comparing pulmo-
nary haemodynamics among these subgroups. As ddI
exposure might cause non-cirrhotic portal hypertensi-
on, we compared HVPG values between patients with
and without ddI exposure and found no significant dif-
f erences between these subgroups (ddI 5.2±3.7 mmHg
versus no ddI 4.1±2.9 mmHg; P=0.312).

Influence of advanced fibrosis on haemodynamic
parameters
Haemodynamic parameters were compared between
patients without advanced fibrosis (META VIR F0–F2;
n=48) and patients with advanced fibrosis (META-
VIR F3/4; n=32; Table 2). Advanced fibrosis was
significantly associated with haemodynamic altera-
tions related to hyperdynamic circulation, as shown
by decreased SysVR (P=0.035) and increased CO
(P=0.008). Mean arterial blood pressure was not sig-
nificantly different between patients with and with-
out advanced fibrosis, indicating a well-compensated
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (±sd)</td>
<td>38 (±10)</td>
</tr>
<tr>
<td>Sex, m/f (% male)</td>
<td>62/18 (78)</td>
</tr>
<tr>
<td>BMI, kg/m² (±sd)</td>
<td>23.3 (±4.1)</td>
</tr>
<tr>
<td>ALT, IU/ml (±sd)</td>
<td>94 (±66)</td>
</tr>
<tr>
<td>Duration of HIV infection, years (±sd)</td>
<td>15 (±6)</td>
</tr>
<tr>
<td>Duration of HIV infection, years (±sd)</td>
<td>14 (±6)</td>
</tr>
<tr>
<td>CD4+ T-cell count, cells/µl (±sd)</td>
<td>509 (±246)</td>
</tr>
<tr>
<td>CD4+ T-cell nadir, cells/µl (±sd)</td>
<td>284 (±172)</td>
</tr>
<tr>
<td>cART, n (%)</td>
<td>59 (74)</td>
</tr>
<tr>
<td>NNRTI, n (%)</td>
<td>75 (91)</td>
</tr>
<tr>
<td>PI, n (%)</td>
<td>32 (40)</td>
</tr>
<tr>
<td>Previous didanosine exposure, n (%)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Didanosine exposure, months (±sd)</td>
<td>16 (±11)</td>
</tr>
<tr>
<td>HCV genotype</td>
<td></td>
</tr>
<tr>
<td>1, n</td>
<td>43</td>
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<tr>
<td>2, n</td>
<td>2</td>
</tr>
<tr>
<td>3, n</td>
<td>23</td>
</tr>
<tr>
<td>4, n</td>
<td>10</td>
</tr>
<tr>
<td>5, n</td>
<td>0</td>
</tr>
<tr>
<td>6, n</td>
<td>1</td>
</tr>
<tr>
<td>Prevalence of HCV genotype 1/4, n (%)</td>
<td>53 (66)</td>
</tr>
<tr>
<td>HCV RNA, log IU/ml (±sd)</td>
<td>6.65 (±0.21)</td>
</tr>
<tr>
<td>Prevalence of high viral load (&gt;800,000 IU/ml), n (%)</td>
<td>54 (68)</td>
</tr>
<tr>
<td>Median hepatic necroinflammatory activity, METAVIR A (range)</td>
<td>0 to 2</td>
</tr>
<tr>
<td>Median liver fibrosis stage, METAVIR F (range)</td>
<td>0 to 4</td>
</tr>
<tr>
<td>Advanced fibrosis METAVIR F3/4, n (%)</td>
<td>32 (40)</td>
</tr>
<tr>
<td>Liver stiffness, kPa (±sd)</td>
<td>10.5 (±6.2)</td>
</tr>
<tr>
<td>Portal pressure (HVPg), mmHg (±sd)</td>
<td>4.7 (±3.6)</td>
</tr>
<tr>
<td>Portal hypertension (HVPg≥5 mmHg), n (%)</td>
<td>21 (26)</td>
</tr>
<tr>
<td>CSPH (HVPg≥10 mmHg), n (%)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Hyperdynamic circulation (CI≥4.5 l/min and SysPV≥600 dyn s/cm²), n (%)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>PAP mean, mmHg (±sd)</td>
<td>14.8 (±4.2)</td>
</tr>
<tr>
<td>Elevated pulmonary pressure (PAP mean ≥20 mmHg), n (%)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension (PAP mean &gt;25 mmHg), n (%)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Portopulmonary hypertension (HVPg≥10 mmHg and PAP mean ≥25 mmHg), n (%)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Values are mean (±sd) unless otherwise indicated. ALT, alanine aminotransferase; BMI, body mass index; cART, combination antiretroviral therapy; CI, cardiac index; CSPH, clinically significant portal hypertension; HVPg, hepatic venous pressure gradient; NNRTI, non-nucleoside reverse transcriptase inhibitor; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; PAP mean, mean pulmonary arterial pressure; PI, protease inhibitor; SysPV, systemic vascular resistance.

Effects of PEG-IFN-α+RBV therapy on haemodynamic parameters

A total of 31 patients had a second follow-up evaluation of systemic, pulmonary and hepatic haemodynamics after completion of antiviral therapy with PEG-IFN-α+RBV. No significant changes were noted in systemic (CO, SysVR) or pulmonary (PAP, PuVR) parameters after PEG-IFN-α+RBV therapy. We found a significant decrease in portal pressure of -21% (P=0.013).

Overall sustained virological response (SVR) to PEG-IFN-α+RBV in patients with follow-up measurements was 45% (14/31), whereas 55% (17/31) experienced virological relapse after antiviral therapy or were non-responders. Only patients with HCV clearance after antiviral therapy showed a significant decrease in portal pressure (mean -29%; P<0.001; Figure 1A), whereas patients without HCV eradication had a non-significant decrease of portal pressure (mean -8%; P=0.261; Figure 1B; Table 4). Notably, one patient with CSPH (HVPg of 11 mmHg at screening) showed a decrease in HVPg to 6 mmHg after completing antiviral therapy. In another two out of four patients with elevated portal pressure (HVPg 6–9 mmHg) at screening, portal pressure returned to values within the normal range after HCV eradication by antiviral therapy with PEG-IFN-α+RBV.

Among the three patients with PAH, PAP mean normalized in one patient, decreased below a PAP mean of 25 mmHg (but remained ≥20 mmHg) in one patient and remained ≥25 mmHg in one patient. Notably, the patient with PPHTN showed both a significant decrease in HVPG state of cirrhosis (all patients with METAVIR F4 were Child–Pugh A). Interestingly, PAP mean was significantly higher (P=0.027) in HIV–HCV-coinfected patients with advanced fibrosis than in patients without advanced fibrosis. This was primarily caused by higher systolic PAP values (P=0.067) rather than by higher diastolic PAP values (P=0.142). PuVR was increased in patients with advanced fibrosis (P=0.022). PAH (including PPHTN) and PHT were only diagnosed in cirrhotic patients and not in patients without significant fibrosis.

Risk factors for hyperdynamic circulation and PAH

When comparing baseline parameters of patients with and without hyperdynamic circulation, we found that fibrosis stage (P=0.025), liver stiffness (P=0.004) and portal pressure (P=0.002) were significantly associated with hyperdynamic circulation (Table 3). A trend towards a higher prevalence of past alcohol abuse (75% versus 38%; P=0.109) and higher HIV viraemia (10,720 versus 5,164 copies/ml; P=0.125) was also recorded in patients presenting with hyperdynamic circulation.

Higher fibrosis stage (P=0.015) and liver stiffness (P=0.003), as well as increased portal pressure (P=0.012), were all significantly associated with elevated pulmonary arterial pressure. As for hyperdynamic circulation, a non-significant trend was observed for higher HIV viraemia (P=0.106) and for lower CD4+ T-cell counts (P=0.081) in HIV–HCV-coinfected patients with PAP mean ≥20 mmHg.
Table 2. Haemodynamic parameters according to fibrosis stage

| Parameter                        | All (n=80) | F1/F2 (n=48) | F3/F4 (n=32) | P-value *
|----------------------------------|------------|--------------|--------------|--------
| **Systemic haemodynamics**       |            |              |              |        
| Heart rate, bpm (±s.o.)          | 71 (±12)   | 69 (±12)     | 72 (±10)     | 0.175  
| ABP_syst, mmHg (±s.o.)           | 120 (±16)  | 123 (±16)    | 117 (±16)    | 0.895  
| ABP_diast, mmHg (±s.o.)          | 77 (±11)   | 79 (±10)     | 75 (±12)     | 0.849  
| MAP, mmHg (±s.o.)                | 92 (±12)   | 94 (±11)     | 89 (±13)     | 0.887  
| SypVR, dyn s/cm² (±s.o.)         | 1,306 (±372) | 1,722 (±414) | 1,016 (±273) | 0.035  
| Cardiac output, l/min (±s.o.)    | 6.15 (±1.46) | 5.81 (±1.38) | 6.76 (±1.50) | 0.008  
| Cardiac index, l/min/m² (±s.o.)  | 3.59 (±0.70) | 3.24 (±0.65) | 3.78 (±0.71) | 0.048  
| Stroke volume, ml (±s.o.)        | 89 (±23)   | 85 (±22)     | 94 (±22)     | 0.090  
| CVP, mmHg (±s.o.)                | 3.8 (±2.6) | 3.8 (±2.6)   | 3.8 (±2.7)   | 0.926  
| **Pulmonary haemodynamics**      |            |              |              |        
| PAP_syst, mmHg (±s.o.)           | 20.0 (±4.9) | 17.6 (±3.4)  | 21.3 (±5.5)  | 0.067  
| PAP_diast, mmHg (±s.o.)          | 10.5 (±4.1) | 9.6 (±3.3)   | 11.7 (±5.2)  | 0.142  
| PAP_mean, mmHg (±s.o.)           | 14.8 (±4.2) | 12.8 (±3.5)  | 16.3 (±5.1)  | 0.027  
| PuVR, dyn s/cm² (±s.o.)          | 119 (±67)  | 88 (±46)     | 142 (±81)    | 0.022  
| PCWP, mmHg (±s.o.)               | 6.9 (±2.7) | 6.3 (±2.7)   | 7.7 (±2.6)   | 0.083  
| **Hepatic haemodynamics**        |            |              |              |        
| HVPG, mmHg (±s.o.)               | 4.7 (±3.6) | 2.9 (±0.9)   | 7.4 (±4.5)   | <0.0001

Values are mean (±s.o) unless otherwise indicated. *Comparing F1/2 versus F3/4. ABP_syst, systolic arterial blood pressure; ABP_diast, diastolic arterial blood pressure; CVP, central venous pressure; HVPG, hepatic venous pressure gradient; MAP, mean arterial blood pressure; PAP_syst, systolic pulmonary arterial pressure; PAP_diast, diastolic pulmonary arterial pressure; PAP_mean, mean pulmonary arterial pressure; PuVR, pulmonary vascular resistance; SypVR, systemic vascular resistance.

Table 3. Parameters associated with hyperdynamic circulation and PAH

| Parameters                  | Hyperdynamic circulation < 4 months (n=40) | Hyperdynamic circulation > 4 months (n=76) | Elevated pulmonary pressure < 60 mmHg (n=80) | Elevated pulmonary pressure > 60 mmHg (n=72) | P-value *
|-----------------------------|------------------------------------------|------------------------------------------|---------------------------------------------|---------------------------------------------|--------
| Age, years (±s.o.)          | 42 (±5)                                  | 38 (±10)                                 | 39 (±9)                                     | 38 (±10)                                   | 0.735  
| Sex, m/f (% male)           | 3(175)                                   | 59/17 (78)                               | 7 (11)                                      | 55/17 (76)                                 | 0.696  
| BMI, kg/m² (±s.o.)          | 22.3 (±5.4)                              | 23.4 (±4.1)                              | 25.7 (±6.5)                                | 23.1 (±3.8)                                | 0.330  
| Prior alcohol abuse, n (%)  | 30 (11)                                  | 28 (31)                                  | 30 (11)                                     | 26 (32)                                    | 0.539  
| Smokers, n (%)              | 2 (50)                                   | 6 (51)                                   | 6 (25)                                      | 5 (25)                                      | 0.665  
| Didanosine exposure, n (%)  | 1 (25)                                   | 6 (8)                                    | 2 (25)                                      | 5 (25)                                      | 0.118  
| ALT, IU/ml (±s.o.)          | 77 (±27)                                 | 53 (±18)                                 | 92 (±88)                                    | 83 (±65)                                    | 0.673  
| CD4+ T-cell count, cells/μl (±s.o.) | 417 (±203)                           | 498 (±247)                               | 384 (±170)                                 | 523 (±249)                                 | 0.081  
| cART, n (%)                 | 3 (75)                                   | 56 (74)                                  | 56 (74)                                     | 56 (74)                                     | 0.47  
| HIV RNA, copies/ml (±s.o.)  | 10,720 (±2,020)                          | 5,164 (±1,310)                           | 17,340 (±905)                               | 5,004 (±386)                               | 0.106  
| HCV RNA, log IU/ml (±s.o.)  | 6.52 (±0.41)                             | 6.66 (±0.52)                             | 6.69 (±0.13)                                | 6.65 (±0.22)                                | 0.477  
| Median fibrosis stage, (%)  | 4 (3–4)                                  | 2 (0–4)                                  | 3 (2–4)                                     | 2 (0–4)                                    | 0.015  
| METAVIR (range)             |                                         |                                          |                                             |                                             |        
| Liver stiffness, kPa (±s.o.) | 36.7 (±10.7)                             | 9.6 (±9.9)                               | 28.1 (±16.5)                                | 8.5 (±5.3)                                  | 0.003  
| Portal pressure, mmHg (±s.o.)| 10.6 (±5.3)                              | 4.3 (±3.2)                               | 8.6 (±7.7)                                  | 4.2 (±2.6)                                  | 0.012  

Values are mean (±s.o) unless otherwise indicated. *Cardiac index > 5 l/min/m² and systemic vascular resistance < 600 dyn s/cm². Mean pulmonary arterial pressure (PAP_mean) > 20 mmHg. ALT, alanine aminotransferase; BMI, body mass index; cART, combination antiretroviral therapy; PAH, pulmonary arterial hypertension.

(11 mmHg to 6 mmHg) and in PAP_mean (27 mmHg to 19 mmHg) after achieving SVR to PEG-IFN-α+RBV therapy.

Discussion

This is the first study reporting prospective data on the prevalence of hepatic, pulmonary and systemic hemodynamic alterations in the ‘high-risk’ group of HIV–HCV-coinfected patients. Advanced fibrosis (METAVIR fibrosis stage 3 or 4) seems to be associated with increased PAP_mean and hyperdynamic circulation. The prevalence of PHT in unselected HIV–HCV-coinfected patients was found to be as high as 26%, whereas CSPH was present in 6% of coinfected patients presenting for evaluation of antiviral therapy. Hyperdynamic circulation was found in 5% of patients and all of them had CSPH as...
assessed by HVPG measurement. The overall prevalence of PAH was low: 4% in our cohort of HIV–HCV-coinfected patients. Interestingly, two of three patients had PAH that was HIV-related and they were diagnosed with HIV-PAH, whereas one patient had PPHTN.

To reduce possible selection bias, most HIV–HCV-coinfected patients without invasive haemodynamic measurements were non-invasively evaluated for CSPH and PAH by abdominal ultrasound and echocardiography, which did not increase the prevalence of suspected

Table 4. Haemodynamic effects of antiviral therapy with PEG-IFN+RBV<sup>a</sup>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before AVT</th>
<th>After AVT</th>
<th>Mean change, %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm (±sd)</td>
<td>71 (±10)</td>
<td>72 (±13)</td>
<td>+1</td>
<td>0.971</td>
</tr>
<tr>
<td>ABP&lt;sub&gt;syst&lt;/sub&gt;, mmHg (±sd)</td>
<td>118 (±10)</td>
<td>124 (±15)</td>
<td>+5</td>
<td>0.253</td>
</tr>
<tr>
<td>ABP&lt;sub&gt;dias&lt;/sub&gt;, mmHg (±sd)</td>
<td>76 (±8)</td>
<td>79 (±11)</td>
<td>+4</td>
<td>0.692</td>
</tr>
<tr>
<td>MAP, mmHg (±sd)</td>
<td>90 (±8)</td>
<td>94 (±12)</td>
<td>+4</td>
<td>0.382</td>
</tr>
<tr>
<td>SysVR, dyn s/cm² (±sd)</td>
<td>1,144 (±248)</td>
<td>1,160 (±243)</td>
<td>+2</td>
<td>0.564</td>
</tr>
<tr>
<td>Cardiac output, l/min (±sd)</td>
<td>6.4 (±1.1)</td>
<td>6.5 (±1.1)</td>
<td>+2</td>
<td>0.454</td>
</tr>
<tr>
<td>Cardiac index, l/min/m² (±sd)</td>
<td>3.5 (±0.5)</td>
<td>3.6 (±0.6)</td>
<td>+1</td>
<td>0.454</td>
</tr>
<tr>
<td>Stroke volume, ml/beat (±sd)</td>
<td>91 (±20)</td>
<td>92 (±19)</td>
<td>+1</td>
<td>0.909</td>
</tr>
<tr>
<td>CVP, mmHg (±sd)</td>
<td>3.5 (±2.5)</td>
<td>3.7 (±2.2)</td>
<td>+6</td>
<td>0.411</td>
</tr>
<tr>
<td>PAP&lt;sub&gt;syst&lt;/sub&gt;, mmHg (±sd)</td>
<td>18.6 (±4.2)</td>
<td>18.2 (±4.3)</td>
<td>-2</td>
<td>0.710</td>
</tr>
<tr>
<td>PAP&lt;sub&gt;dias&lt;/sub&gt;, mmHg (±sd)</td>
<td>10.2 (±3.9)</td>
<td>9.5 (±3.3)</td>
<td>-6</td>
<td>0.256</td>
</tr>
<tr>
<td>PAP&lt;sub&gt;mean&lt;/sub&gt;, mmHg (±sd)</td>
<td>13.6 (±4.0)</td>
<td>13.3 (±3.3)</td>
<td>-2</td>
<td>0.693</td>
</tr>
<tr>
<td>PuVR, dyn s/cm² (±sd)</td>
<td>98 (±57)</td>
<td>88 (±42)</td>
<td>-10</td>
<td>0.117</td>
</tr>
<tr>
<td>PCWP, mmHg (±sd)</td>
<td>7.1 (±3.2)</td>
<td>6.9 (±2.5)</td>
<td>-3</td>
<td>0.820</td>
</tr>
<tr>
<td>HVPG, mmHg (±sd)</td>
<td>4.2 (±2.2)</td>
<td>3.3 (±1.7)</td>
<td>-21</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Values are mean (±sd) unless otherwise indicated. *A total of 31 patients with follow-up haemodynamic evaluation. ABP<sub>syst</sub>, diastolic arterial blood pressure; ABP<sub>dias</sub>, systolic arterial blood pressure; AVT, antiviral therapy; CVP, central venous pressure; HVPG, hepatic venous pressure gradient; MAP, mean arterial blood pressure; PAP<sub>syst</sub>, diastolic pulmonary arterial pressure; PAP<sub>dias</sub>, mean pulmonary arterial pressure; PAP<sub>mean</sub>, systolic pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PEG-IFN, pegylated interferon; PuVR, pulmonary vascular resistance; RBV, ribavirin; SysVR, systemic vascular resistance.

Effects of antiviral therapy with pegylated interferon plus ribavirin on portal pressure in patients (A) with HCV clearance and (B) without HCV clearance. Symbols indicate individual patients. HVPG, hepatic venous pressure gradient.

Figure 1. Course of portal pressure before and after antiviral therapy

To reduce possible selection bias, most HIV–HCV-coinfected patients without invasive haemodynamic measurements were non-invasively evaluated for CSPH and PAH by abdominal ultrasound and echocardiography, which did not increase the prevalence of suspected...
Interestingly, the prevalence of PAH was low at 4%, the risk group of HIV–HCV coinfected patients so hyperdynamic circulation. The prevalence of PAH has not been reported for CSPH or PAH in these patients. In addition, we did not find any relationship between smoking habits and the prevalence of PAH in our study population. Exposure to ddI was associated with elevated portal pressure, although (pre-sinusoidal) non-cirrhotic portal hypertension might not be adequately assessed by measurement of HVPG.

An overall SVR rate of 45% was achieved. However, the flat doses of RBV (at the time of study design there were concerns about potential drug–drug interactions of cART and RBV) and 48 weeks treatments in some HIV–HCV genotype 1/4 patients with unfavourable baseline/on-treatment’ characteristics might have impaired SVR rates.

As haemodynamic alterations in patients with chronic HCV infection normally develop in stages of more advanced liver disease, we compared haemodynamic parameters of patients with bridging cirrhosis and cirrhosis (METAVIR F3/4) with patients without cirrhosis (METAVIR F0–F2). As expected, portal pressure was significantly higher in patients with advanced fibrosis with 26% and 6% of patients presenting with PHT and CSPH, respectively (all with advanced fibrosis).

When evaluating the risk factors for hyperdynamic circulation, we found (as suspected) a correlation with histological fibrosis stage, liver stiffness and portal pressure. A non-significant association of hyperdynamic circulation with a history of alcohol abuse, higher alanine aminotransferase levels and higher HIV RNA levels was found in our HIV–HCV-coinfected patients. These findings indicate that more active liver disease, either induced by alcoholic damage or by a more aggressive course of HCV (reflected by increased alanine aminotransferase levels) possibly as a consequence of uncontrolled HIV infection (as suggested by HIV viraemia [30]), leads to advanced fibrosis and aggravates hyperdynamic circulation.

The prevalence of PAH has not been reported for the risk group of HIV–HCV coinfected patients so far, who could suffer from both HIV-PAH or PPHTN. Interestingly, the prevalence of PAH was low at 4%, although 10% of patients presented with elevated pulmonary arterial pressure. Notably, only one of three cases with PAH was attributed to PPHTN, whereas two were HIV-PAH. Nevertheless, liver disease and portal hypertension appear to influence pulmonary haemodynamics, as patients with advanced fibrosis had significantly higher PAP values and significantly higher PuVR than patients without advanced fibrosis. When comparing patients with elevated pulmonary arterial pressure to patients with normal pulmonary haemodynamics, we found that fibrosis stage, liver stiffness and portal pressure were all associated with elevated pulmonary arterial pressure. As for hyperdynamic circulation, a non-significant trend towards lower CD4+ T-cell count and higher HIV viraemia was noted in patients with elevated PAP values. Considering that in our study we had both patients with HIV-PAH and PPHTN, a multifactorial aetiology of PAH including elevated portal pressure, advanced fibrosis, HIV viraemia and lower CD4+ T-cell counts, as well as thromboembolic events secondary to intravenous drug injection, might be responsible for the alterations in pulmonary haemodynamics observed in our HIV–HCV-coinfected cohort.

Furthermore, we confirmed prior data on the beneficial effects of antiviral therapy on portal pressure in HCV-monoinfected patients [31], as PEG-IFN-α+RBV therapy also decreased portal pressure in HIV–HCV-coinfected patients. Of note, this decrease in portal pressure was only significant for patients who achieved SVR with eradication of HCV infection. Most importantly, antiviral therapy did not significantly influence portal pressure in virological relapsers or non-responders. As HCV eradication has been reported to decrease pro-inflammatory cytokines and to ameliorate endothelial dysfunction in HIV–HCV-coinfected patients [23], we also assessed the influence of antiviral therapy on systemic and pulmonary haemodynamics in a subgroup of coinfected patients. No clear effects of PEG-IFN-α+RBV on pulmonary arterial pressure and pulmonary vascular resistance nor on systemic haemodynamics were observed, but this might be due to the low prevalence of hyperdynamic circulation and PAH in our study population. However, in one patient with HIV-PAH the PAP values was decreased to <25 mmHg (but remained >20 mmHg), whereas the PAP was reduced to <20 mmHg in a patient with PPHTN after achieving SVR.

In summary, we found a high prevalence of PHT but a low prevalence of hyperdynamic circulation in HIV–HCV-coinfected patients. Risk factors for hyperdynamic circulation include advanced fibrosis, increased liver stiffness and portal hypertension, although HIV viraemia and alcohol could be involved in the pathophysiology of hyperdynamic circulation. Both HIV-PAH and PPHTN can occur in HIV–HCV-coinfected patients, but the overall prevalence seems to be low. Advanced fibrosis, increased liver stiffness and portal pressure represent clear risk factors for PAH in HIV–HCV-coinfected patients, while PAH should also be considered in patients with high HIV RNA levels and low CD4+ T-cell counts. HCV eradication by antiviral therapy with PEG-IFN-α+RBV decreases portal pressure, but does not seem to have a significant effect on pulmonary or systemic haemodynamic alterations in patients with HIV–HCV coinfection.

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measurements (TR, BAP, AF, WS, MP-R), acquisition of data (TR, BAP, PB, MCA, BS, AK), analysis and interpretation of data (TR, MT, MP-R), drafting of the manuscript (TR, MP-R), critical revision of the manuscript for important intellectual content (TR, BAP, AF, WS, BS, AR, MT, MP-R) and statistical analysis (TR).

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References

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