High arterial compliance in cirrhosis is related to low adrenaline and elevated circulating calcitonin gene related peptide but not to activated vasoconstrictor systems

J H Henriksen, S Møller, S Schifter, J Abrahamsen, U Becker

Abstract

Background and aims—Static and dynamic functions of the wall of large arteries are largely unknown in cirrhosis in vivo. The present study was undertaken to determine arterial compliance (COMP<sub>aw</sub>) in relation to vasodilator and vasoconstrictor systems in patients with cirrhosis. In addition, vasoactivity was manipulated by inhalation of oxygen.

Study population and methods—In 20 patients with alcoholic cirrhosis and 12 controls we determined COMP<sub>aw</sub> (stroke volume relative to pulse pressure), cardiac output, plasma volume, systemic vascular resistance, central circulation time, plasma catecholamines, renin activity, endothelin-1, and calcitonin gene related peptide (CGRP) at baseline and during oxygen inhalation.

Results—COMP<sub>aw</sub> was significantly increased in cirrhotic patients compared with controls (1.32 v. 1.06 ml/mm Hg; p<0.05) and inversely related to plasma adrenaline levels (r=−0.53; p<0.02) but positively related to circulating levels of CGRP (r=0.58; p<0.01). No significant relation was found for plasma noradrenaline, renin activity, or endothelin-1. COMP<sub>aw</sub> was positively related to plasma volume (r=0.50; p<0.02) and inversely to systemic vascular resistance (r=−0.69; p<0.001) and central circulation time (r=−0.49; p<0.02). During oxygen inhalation, COMP<sub>aw</sub> decreased (−13%; p<0.005) and systemic vascular resistance increased (+10%; p<0.001) towards normal values without significant changes in mean arterial pressure. Plasma adrenaline (−16%; p<0.01) decreased and the relation to COMP<sub>aw</sub> disappeared. The relation of COMP<sub>aw</sub> to CGRP and circulatory variables remained unchanged.

Conclusion—Elevated arterial compliance in cirrhosis is related to low adrenaline, high CGRP, and systemic hyperdynamics but not to indicators of the activated vasoconstrictor systems (noradrenaline, renin, endothelin-1). Thus the altered static and dynamic characteristics of the wall of large arteries are intimately associated with circulatory and vasodilatory derangement in cirrhosis but biomanipulation indicates that the changes are, at least in part, reversible during isobaric conditions.

Keywords: arterial compliance; calcitonin gene related peptide; catecholamines; endothelin 1; hypoxia; renin; systemic vascular resistance

In cirrhosis the circulation is hyperkinetic with increased cardiac output (CO) and plasma volume and decreased systemic vascular resistance and arterial blood pressure. According to the “peripheral artery vasodilatation hypothesis”, systemic vasodilatation leads to arterial underfilling and activation of compensatory vasoactive and homoeostatic mechanisms.

Thus the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), and endothelin system (ETS) are activated in addition to increased neuropituitary release of vasopressin. Apart from an abnormal balance between vasodilatation and vasoconstriction at the arteriolar level, the tonus of larger arteries may be changed. Overall arterial compliance (that is, change in luminal arterial volume relative to change in transmural arterial pressure), a variable of clinical significance in cardiovascular disease, can be assessed as stroke volume relative to pulse pressure. Determined thus, we recently reported that arterial compliance was increased in patients with decompensated cirrhosis, a finding that would indicate changes in static arterial wall composition or dynamic changes in smooth muscle tone, and we hypothesised a relation to elevated circulating levels of the vasodilator calcitonin gene related peptide (CGRP). The relation between arterial compliance, powerful vasoconstrictor systems (SNS, RAAS, ETS), and haemodynamics is unknown in patients with cirrhosis, and there are no reports on isobaric manipulation of arterial compliance in these patients. Hence the present study was undertaken to determine variation in arterial compliance with circulating levels of catecholamines, renin, and endothelin-1, and also to establish a relation with CGRP. Moreover, we manipulated vascular tonus by inhalation of oxygen to evaluate
potential dynamic changes in relation to circulating levels of vasoactive substances.

**Patients and methods**

**STUDY POPULATION**

The study population comprised 20 patients with cirrhosis referred for haemodynamic investigation in order to diagnose and quantify portal hypertension. All patients had biopsy proven cirrhosis. The age range was 34–67 years (mean 51). All had a history of alcohol abuse (that is, consumption exceeding 50 g/day for more than five years). None had experienced recent gastrointestinal bleeding or had encephalopathy greater than grade I. All patients abstained from alcohol and had no withdrawal symptoms at the time of the study. According to the modified Child-Turcotte classification, five were class A patients, six class B, and nine class C. Clinical and biochemical characteristics are summarised in table 1. None of the patients had signs of heart failure, diabetes, cancer, or other major disease. Ultrasonography showed ascites in 12 patients and they received diuretics (spiromolactone 100 mg and furosemide 40–80 mg/day) during withdrawal symptoms at the time of the study. According to the modified Child-Turcotte classification, five were class A patients, six class B, and nine class C. Clinical and biochemical characteristics are summarised in table 1. None of the patients had signs of heart failure, diabetes, cancer, or other major disease. Ultrasonography showed ascites in 12 patients and they received diuretics (spironolactone 100 mg and furosemide 40–80 mg/day) and were started on a sodium restricted diet of 40 mmol/day. None of the patients received any cardiovascular or vasoactive medication. The diet of the eight patients without fluid retention was not restricted.

The control group comprised 12 patients undergoing diagnostic catheterisation for suspicion of intestinal ischaemia, although uncon-"
Central circulation time was determined as the weighted time average of the \(^{99}\text{Tc}\) indicator dilution curve, as described elsewhere.\(^{16,17}\)

**BIOCHEMICAL ANALYSIS**

Routine biochemical tests were performed in an autoanalyser (SMAC; Technicon Instruments, Tarrytown, New York, USA). Data on bioactive substances have been published in part.\(^{14}\)

Analysis of CGRP was performed by radioimmunoassay, as previously described.\(^{14,18}\) The detection limit was 1 pmol/l, and intra- and interassay coefficients of variation were 4% and 7%, respectively. Noradrenaline and adrenaline were determined by high performance liquid chromatography, as previously described.\(^{14,19}\) The detection limit was 10 pg/ml, and intra- and interassay coefficients of variation were less than 9% for both analyses.

Plasma renin activity was determined by an assay involving generation of angiotensin I, as described elsewhere.\(^{14}\) The detection limit was 4 nU/l, and intra- and interassay coefficients of variation were 9% and 10%, respectively. Measurement of endothelin-1 was performed by radioimmunoassay, as described previously.\(^{14,20}\) The detection limit was 0.6 pg/ml, and intra- and interassay coefficients of variation were 5% and 8%, respectively.

**Arterial oxygen saturation** and **carbon dioxide tension** were measured by an ABL 300 blood gas analyser and OSM-2 hemoximeter (Radiometer, Copenhagen) as described elsewhere.\(^{14}\)

**PROTOCOL**

Baseline values of COMP\(_{\text{a}}\), arterial blood pressure, heart rate, stroke volume, CO, systemic vascular resistance, plasma volume, and wedged to free hepatic venous pressure

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**Table 2  Haemodynamics and circulating vasoactive substances in controls and in patients with cirrhosis**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=12)</th>
<th>Cirrhosis (n=20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMP(_{\text{a}}) (ml/mm Hg)</td>
<td>1.06 (0.09) [0.00–1.5]</td>
<td>1.32 (0.10) [0.5–2.2]</td>
<td>0.03</td>
</tr>
<tr>
<td>Arterial blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>144 (7) [90–185]</td>
<td>139 (5) [103–175]</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>72 (3) [56–85]</td>
<td>61 (2) [48–80]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>73 (5) [30–100]</td>
<td>78 (4) [44–105]</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (mm Hg)</td>
<td>100 (4) [78–115]</td>
<td>88 (3) [68–120]</td>
<td>0.02</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>5.74 (0.44) [2.7–7.9]</td>
<td>7.48 (0.37) [4.34–9.96]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>75 (4) [50–96]</td>
<td>79 (3) [56–108]</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>77 (5) [59–101]</td>
<td>97 (6) [60–141]</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Plasma volume (l)</td>
<td>2.89 (0.17) [2.10–3.95]</td>
<td>3.82 (0.19) [2.47–5.39]</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>(ml/kg)</td>
<td>45 (3) [31–64]</td>
<td>55 (2) [41–70]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Arterial O₂ saturation (%)</td>
<td>98.2 (1.5) [95–100]</td>
<td>97.0 (1.1) [94–99]</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial O₂ tension (kPa)</td>
<td>11.1 (0.56) [9.2–13]</td>
<td>11.0 (0.33) [5.7–15]</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial CO₂ tension (kPa)</td>
<td>5.10 (0.18) [4.3–5.8]</td>
<td>4.34 (0.13) [3.4–5.2]</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Wedged to free hepatic vein pressure (mm Hg)</td>
<td>3.4 (1.0) [2–6]</td>
<td>17 (1.5) [5–27]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma noradrenaline (nmol/l)</td>
<td>371 [133–663]</td>
<td>660 (79) [60–1215]</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Plasma adrenaline (nmol/l)</td>
<td>94 [24–199]</td>
<td>177 (23) [46–503]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Plasma renin activity (U/l)</td>
<td>33 [6–59]</td>
<td>656 (273) [4–4813]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma endothelin 1 (pg/ml)</td>
<td>1.5 [0.8–2.1]</td>
<td>7.3 (1.1) [4.3–21.4]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma CGRP (pmol/l)</td>
<td>37 [24–50]</td>
<td>142 (46) [28–944]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Mean (SEM) [range].

COMP\(_{\text{a}}\), arterial compliance; CGRP, calcitonin gene related peptide; CO, cardiac output.

**Figure 1** (A) Arterial compliance (COMP\(_{\text{a}}\)), and arterial oxygen (pO₂ ) and carbon dioxide (pCO₂ ) tensions, and (B) systemic vascular resistance (SVR) in patients with cirrhosis during baseline conditions and oxygen inhalation. Values are mean (SEM).
were determined while subjects breathed room air. Blood samples for oxygen and carbon dioxide tension, and vasoactive peptides and amines were collected from the femoral artery. As oxygen alters haemodynamics and modifies release of vasoactive substances, an oxygen mask was subsequently placed over the nose and mouth, and oxygen was inhaled for one hour. At the end of this period, the above measurements were repeated.

STATISTICAL EVALUATION
Data are expressed as mean (SEM). Statistical analysis was performed by the unpaired/paired Student’s tests or Mann-Whitney/Wilcoxon rank tests where appropriate. Correlation analysis between independent variables was performed with the Pearson regression test (method of least squares) or by the Spearman rank correlation test; p<0.05 was considered significant.

Results
BASELINE (ROOM AIR)
Haemodynamic results are summarised in table 2. COMPₐ was significantly increased in patients with cirrhosis compared with controls (1.32 ± 1.06 ml/mm Hg; p<0.05).

Mean arterial blood pressure, diastolic pressure, and systemic vascular resistance were significantly decreased in patients with cirrhosis.

Table 3 Correlations between arterial compliance (COMPₐ) and vasoactive substances in patients with cirrhosis breathing room air and oxygen (O₂)

<table>
<thead>
<tr>
<th></th>
<th>Room air (r)</th>
<th>p Value</th>
<th>O₂ (r)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma noradrenaline</td>
<td>−0.20</td>
<td>NS</td>
<td>−0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma adrenaline</td>
<td>−0.53</td>
<td>&lt;0.02</td>
<td>−0.28</td>
<td>0.09</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>0.16</td>
<td>NS</td>
<td>0.29</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma endothelin-1</td>
<td>−0.27</td>
<td>NS</td>
<td>−0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma CGRP</td>
<td>0.58</td>
<td>&lt;0.01</td>
<td>0.47</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

r, correlation under baseline conditions (room air) and O₂ inhalation; CGRP, calcitonin gene related peptide.

Figure 2 Relation between circulating levels of calcitonin gene related peptide (CGRP) and arterial compliance (COMPₐ) in patients with cirrhosis during baseline conditions (filled symbols) and oxygen inhalation (open symbols). Child, Child-Turcotte class A, B, and C (baseline: r=0.58; p<0.01; +oxygen: r=0.47, p<0.01). The cross indicates normal mean (SD) value.

Figure 3 Relation between plasma volume (PV) and arterial compliance (COMPₐ) (baseline: r=0.50; p<0.02; +oxygen: r=0.43, p<0.02). Symbols as in fig 2.

CO, stroke volume, plasma volume, circulating CGRP, adrenaline, noradrenaline, renin activity, and endothelin-1 were significantly increased.

OXYGEN INHALATION
As illustrated in fig 1, a highly significant decrease (−13%; p<0.005) in COMPₐ was observed during oxygen inhalation whereas systemic vascular resistance increased (+10%; p<0.001). Significant changes in CO (−12%; p<0.005) and stroke volume (−8%; p<0.05) were found but arterial blood pressure was unchanged (+1%; ns).

No significant change was observed in circulating CGRP or endothelin-1 levels during oxygen inhalation. A borderline significant decrease was seen in plasma renin activity (−18%; p=0.07), and circulating adrenaline and noradrenaline decreased significantly (−16% (p<0.01) and −13% (p<0.02), respectively).

RELATION BETWEEN COMPₐ AND VASODILATORS/VASOCONSTRICTORS
During baseline conditions, a significant inverse correlation was found between COMPₐ and plasma adrenaline (r=−0.53; p<0.02) but this disappeared during oxygen inhalation (see table 3). No significant relation was found between systemic vascular resistance and plasma adrenaline (r=−0.05; ns). No significant correlations were established between COMPₐ on the one hand and circulating noradrenaline, renin activity, and endothelin-1 on the other. Oxygen inhalation did not change the absence of significant relations between COMPₐ and these vasoconstrictors. As illustrated in fig 2 and table 3, a significant positive relation was found between COMPₐ and circulating CGRP (r=0.58; p<0.01), and this relation continued during oxygen inhalation (r=0.47; p<0.01).

RELATION TO HEMODYNAMICS
A positive relation was found between COMPₐ and an independent determination of plasma
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Inhalation almost normalises COMPart and RAAS, and endothelin-1 (ETS)); (2) oxygen systems (noradrenaline (SNS), renin activity not to indicators of the potent vasoconstrictor inversely related to circulating adrenaline but arterial compliance (COMPart) in cirrhosis is The present study shows that: (1) elevated Discussion

No relation was found between circulating levels of plasma noradrenaline, renin activity, and endothelin-1 on the one hand and COMPst on the other. These amine/peptides are indicators of potent vasoconstrictor systems. In vitro measurements, animal experiments, and clinical investigations suggest that increased SNS activity and activation of the RAAS and ETS may modulate the tonus of large arteries. Thus the cold pressor test and mental stress, which enhance SNS activity, were followed by a decrease in arterial compliance. In cirrhosis, it is well established that especially in decompensated patients, SNS activity is enhanced and RAAS is overactivated. However, our patients had increased and not decreased COMPst, and no relation was found between these indicators of the vasoconstrictor systems and COMPst or systemic vascular resistance. This suggests defective vascular reactivity (or a
Arterial compliance in cirrhosis

pronounced counterbalancing effect of vasodilating substances—for example, nitric oxide, CGRP), not only at the arteriolar level but also of the wall of large arteries which indicates abnormal static and dynamic characteristics of large arteries in patients with cirrhosis.

The present finding of a direct relation between high COMP\textsubscript{an} and elevated circulating CGRP confirms earlier findings in other patients with cirrhosis from our laboratory.\textsuperscript{12} CGRP is a powerful vasodilator\textsuperscript{17-18} and it is conceivable that it works together with nitric oxide, adrenomedullin, glucagon, prostaglandins, and others in splanchic and peripheral vasodilatation in cirrhosis.\textsuperscript{39-40} Apart from relaxation at the arteriolar level, the present and earlier findings of a relation between COMP\textsubscript{an} and this vasodilator peptide may suggest that CGRP also plays a role in modulation of large vessel tonus,\textsuperscript{12} and this view is supported by recent animal experiments.\textsuperscript{45} Relations to other vasodilators must await further investigations.

It has been shown in normal subjects and patients with different diseases that COMP\textsubscript{an} has a non-linear relation to the level of arterial blood pressure.\textsuperscript{21-23 44 45} However, the present change in COMP\textsubscript{an} during oxygen inhalation was not related to any change in transmural blood pressure level (isobaric condition) or to changes in circulating CGRP or endothelin. The observed decrease in adrenaline may not contribute to decreased COMP\textsubscript{an}, unless it is assumed that adrenaline has a vasodilatory effect on the large arteries in cirrhosis. However, hypoxia is a strong vasodilatory stimulus in itself. Inhalation of oxygen may improve tissue oxygen tension in patients with cirrhosis and thereby arteriolar contraction, and thus contribute to normalisation of otherwise low systemic vascular resistance.\textsuperscript{40-46} A similar mechanism is possible in large arteries, especially if tissue released vasodilators escape the pulmonary circulation into the systemic arterial tree. It is well established that carbon dioxide tension can also modulate vascular tension and sympathetic nervous tone.\textsuperscript{40} However, this mechanism is unlikely to be of major importance as no significant change was observed in arterial carbon dioxide tension during oxygen inhalation. Coupling between COMP\textsubscript{an} and systemic vascular resistance was rather strong and remained after manipulation of both variables (fig 4). This may suggest a common genesis of arteriolar dilatation and altered wall characteristics of the arterial tree in cirrhosis. However, these aspects need further investigation.

COMP\textsubscript{an} was directly related to indicators of the hyperkinetic circulation—that is, plasma volume and central circulation time. As COMP\textsubscript{an} was determined from indicator measurement of radioiodinated albumin, a pseudo correlation might be present if plasma volume and central circulation time were determined by the same indicator. We therefore used an independent technique by injection of \textsuperscript{99m}Tc labelled albumin to determine separately plasma volume and central circulation time. Consequently, the present finding of significant relations is based on statistical analysis of independent variables. Most plasma is located in smaller and larger veins.\textsuperscript{19} Thus it is not evident that the size of the plasma volume bears a relation to arterial wall characteristics. On the other hand, high arterial compliance may contribute to baroreceptor activation of sodium-water retention which may increase plasma volume.\textsuperscript{50 51} A short central circulation time is a prognostic variable in cirrhosis and indicates abnormal distribution of the circulating medium with a small central and arterial blood volume relative to CO.\textsuperscript{57 58} Low systemic vascular resistance and splanchic fistulas may divert arterial blood to the venous side, and this may also contribute to observed increase in COMP\textsubscript{an} as it is well established that diminished filling of the arterial tree increases compliance.\textsuperscript{21 22 53 54}

In conclusion, arterial compliance is elevated in cirrhosis and related to low adrenaline, high circulating CGRP, and to indicators of systemic hyperdynamics (plasma volume, systemic vascular resistance, central circulation time) but not to indicators of the potent vasoconstrictor systems (noradrenaline (SNS), renin activity (RAAS), endothelin-1 (ETS)). The altered static and dynamic characteristics of the wall are closely associated with circulatory and vasodilatory derangement in cirrhosis but biomanipulation indicates that the changes are, at least in part, reversible during isobaric conditions.

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