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>ar</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>ar</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>ar</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>ar</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>ar</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>ar</sub> disappeared. The relation of COMP<sub>ar</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 homeostatic mechanisms.

Thus the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), and endothelin system (ETS) are activated in addition to increased neurosecretory 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 blood pressure), a variable of clinical significance in cardiovascular disease, can be assessed and manipulated 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...

Abbreviations used in this paper: COMP<sub>ar</sub> arterial compliance; CGRP, calcitonin gene related peptide; CO, cardiac output; SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; ETS endothelin system.
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 (spironolactone 100 mg and furosemide 40–80 mg/day) and were started on a sodium restricted diet of the eight patients without fluid retention. 

**Patients and controls underwent liver vein catheterisation which was performed in the morning after an overnight fast and at least one hour in the supine position, as described previously.** In brief, a Cournand catheter (7F) or Swan-Ganz catheter (7F) was guided under local anaesthesia into the right hepatic veins and right atrium through the femoral venous route under fluoroscopic control. A small indwelling polyethylene catheter (5F) was introduced by the Seldinger technique into the femoral artery with its tip at the aortic bifurcation.

**Pressures** were measured with a capacitance transducer (Simonsen and Weel, Copenhagen, Denmark), as previously described. The midaxillary line was taken as zero pressure level. Wedged to free hepatic vein pressure was determined in different vessels and the mean values of repeated measurements were used.

**Systolic arterial blood pressure** was determined as the average of maximum blood pressure over 20–30 seconds, and **diastolic arterial blood pressure** as the minimum pressure. **Pulse pressure**—that is, systolic minus diastolic blood pressure—was measured as the average amplitude of the oscillating pressure over 20–30 seconds. **Mean arterial blood pressure** was determined independently by electronic integration of the pressure signal and referred to an external water column as reference.

**Arterial compliance** (COMP, mHg/ml) was assessed as stroke volume divided by pulse pressure, as described in detail elsewhere. **Stroke volume** was determined as CO divided by heart rate; **CO** was measured by the indicator dilution technique after bolus injection of 150 KBq of 125I labelled human serum albumin (Institute of Energy Technique, Kjeller, Norway) followed by automatic arterial sampling, and heart rate was assessed by ECG.

Plasma volume was determined by another indicator, independent of 125I indicator CO determination. Quantitative injection of 1 MBq 99mTc labelled human serum albumin (Vasculocis, CIS Bio International, Grif-Sur-Yvette, France) was given into the right atrium, followed by automatic arterial sampling for 60 seconds and a sample after 10 minutes, as previously described. **Systemic vascular resistance** (dyn s/cm²) was determined as 80×(mean arterial pressure−atrial pressure) divided by the additionally measured **cardiac output** (CO by the 99mTc indicator), pressures being expressed in mm Hg and CO as l/min.
Central circulation time was determined as the weighted time average of the 99mTc indicator dilution curve, as described elsewhere.\textsuperscript{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.\textsuperscript{14}

Analysis of CGRP was performed by radioimmunoassay, as previously described.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 tension and carbon dioxide tension were measured by an ABL 300 blood gas analyser and OSM-2 hemoximeter (Radiometer, Copenhagen) as described elsewhere.\textsuperscript{14}

**PROTOCOL**

Baseline values of COMP\textsubscript{art}, arterial blood pressure, heart rate, stroke volume, CO, systemic vascular resistance, plasma volume, and wedged to free hepatic venous pressure were determined as the weighted time average of the 99mTc indicator dilution curve, as described elsewhere.\textsuperscript{16, 17}

### 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>COMPart (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>NS</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) [4.5–4.96]</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) [39–101]</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>3.62 (0.19) [2.47–5.39]</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Arterial O\textsubscript{2} 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 O\textsubscript{2} tension (kPa)</td>
<td>11.1 (0.56) [9.2–15]</td>
<td>11.0 (0.33) [9.8–15]</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial CO\textsubscript{2} 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) [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>658 (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 (48) [28–944]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Mean (SEM) [range].

COMP\textsubscript{art}, arterial compliance; CGRP, calcitonin gene related peptide; CO, cardiac output.

**Figure 1**  (A) Arterial compliance (COMP\textsubscript{art}), and arterial oxygen (pO\textsubscript{2}) and carbon dioxide (pCO\textsubscript{2}) 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. COMP\textsubscript{ar} 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.

RELATION BETWEEN COMP\textsubscript{ar} AND VASODILATORS/VASOCONSTRICTORS
During baseline conditions, a significant inverse correlation was found between COMP\textsubscript{ar} 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 COMP\textsubscript{ar} 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 COMP\textsubscript{ar} and these vasoconstrictors. As illustrated in fig 2 and table 3, a significant positive relation was found between COMP\textsubscript{ar} and circulating CGRP (r=0.58; p<0.01), and this relation continued during oxygen inhalation (r=0.47; p<0.01).

RELATION TO HAEMODYNAMICS
A positive relation was found between COMP\textsubscript{ar} and an independent determination of plasma

Table 3 Correlations between arterial compliance (COMP\textsubscript{ar}) and vasoactive substances in patients with cirrhosis breathing room air and oxygen (O\textsubscript{2}).

<table>
<thead>
<tr>
<th>COMP\textsubscript{ar} versus</th>
<th>Room air (r)</th>
<th>p Value</th>
<th>O\textsubscript{2} (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 O\textsubscript{2} inhalation; CGRP, calcitonin gene related peptide.

Figure 2 Relation between circulating levels of calcitonin gene related peptide (CGRP) and arterial compliance (COMP\textsubscript{ar}) 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 (COMP\textsubscript{ar}) (baseline: r=0.50; p<0.02; +oxygen: r=0.43, p<0.02). Symbols as in fig 2.

CO\textsubscript{2}, 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 COMP\textsubscript{ar} 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).

Figure 3 shows the relation between plasma volume (PV) and arterial compliance (COMP\textsubscript{ar}) (baseline: r=0.50; p<0.02; +oxygen: r=0.43, p<0.02). Symbols as in fig 2.
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Discussion

The present study shows that: (1) elevated arterial compliance (COMP$_{\text{art}}$) in cirrhosis is inversely related to circulating adrenaline but not to indicators of the potent vasoconstrictor systems (noradrenaline (SNS), renin activity (RAAS), and endothelin-1 (ETS)); (2) oxygen inhalation almost normalises COMP$_{\text{art}}$ and increases systemic vascular resistance with a significant inverse relation between compliance and resistance without changes in mean arterial blood pressure; (3) increased COMP$_{\text{art}}$ is significantly related to indicators of circulatory hyperdynamics (plasma volume, central circulation time); and (4) a direct relation with elevated circulating levels of CGRP is confirmed.

The concept of arterial compliance is complex and wall characteristics of large and small arteries may be different. In the last few years attention has focused on large artery mechanics in cardiovascular disease and disorders with changes in arterial blood pressure. Arterial compliance is an important determinant of afterload which is likely to add to our understanding of the coupling between the heart and arterial system. Moreover, measurement of arterial compliance can be performed in vivo. Most investigations on large vessels have hitherto been performed in experimental cirrhosis and in vitro settings.

Compliance can be determined in a specific segment of the arterial tree or as total arterial compliance. It has recently been substantiated in a large population group that an index of total arterial compliance can be derived as the ratio between stroke volume and pulse pressure, as applied in the present study, where COMP$_{\text{art}}$ in the main reflects compliance of large arteries.

An inverse relation between COMP$_{\text{art}}$ and circulating adrenaline was found in the present study. Adrenaline is a hormone which acts as a vasoconstrictor at high plasma concentrations but at lower concentrations it may have both vasodilatory and vasoconstrictive properties in different vessels. This may obscure an integral reaction and accordingly we did not find any relation to systemic vascular resistance. However, large arteries may react more uniformly to this circulating hormone. As vascular areas differ in their sensitivity to vasoactive substances, a different relationship between COMP$_{\text{art}}$ and adrenaline and locally acting vasoconstrictors, such as noradrenaline and endothelin-1, may be expected, but other explanations such as post-receptor defects and opposing effects of local vasodilators should also be considered.

No relation was found between circulating levels of plasma noradrenaline, renin activity, and endothelin-1 on the one hand and COMP$_{\text{art}}$ 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 different vessels. 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 decompenated patients, SNS activity is enhanced and RAAS is overactivated. However, our patients had increased and not decreased COMP$_{\text{art}}$ and no relation was found between these indicators of the vasoconstrictor systems and COMP$_{\text{art}}$ or systemic vascular resistance. This suggests defective vascular reactivity (or a...
pronounced counterbalancing effect of vasodilating substances—for example, nitric oxide, CGRP—more strongly at the arterial 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<sub>art</sub> and elevated circulating CGRP confirms earlier findings in other patients with cirrhosis from our laboratory. CGRP is a powerful vasodilator and it is conceivable that it works together with nitric oxide, adrenomedullin, glucagon, prostaglandins, and others in splanchic and peripheral vasodilatation in cirrhosis. Apart from relaxation at the arteriolar level, the present and earlier findings of a relation between COMP<sub>art</sub> and this vasodilator peptide may suggest that CGRP also plays a role in modulation of large vessel tone, and this view is supported by recent animal experiments. Relations to other vasodilators must await further investigations.

It has been shown in normal subjects and patients with different diseases that COMP<sub>art</sub> has a non-linear relation to the level of arterial blood pressure. However, the present change in COMP<sub>art</sub> 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<sub>art</sub>, 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. 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. 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<sub>art</sub> 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<sub>art</sub> was directly related to indicators of the hyperkinetic circulation—that is, plasma volume and central circulation time. As COMP<sub>art</sub> was determined from indicator measurement of radiiodinated 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 99mTc 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. 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. 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. Low systemic vascular resistance and splanchic fistulas may divert arterial blood to the venous side, and this may also contribute to the observed increase in COMP<sub>art</sub> as it is well established that diminished filling of the arterial tree increases compliance.

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 may be 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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