Alterations in mechanical properties of mesenteric resistance arteries in experimental portal hypertension

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Resch M, Wiest R, Moleda L, Fredersdorf S, Stoelcker B, Schroeder JA, Schölmerich J, Endemann DH. Alterations in mechanical properties of mesenteric resistance arteries in experimental portal hypertension. Am J Physiol Gastrointest Liver Physiol 297: G849–G857, 2009. First published August 20, 2009; doi:10.1152/ajpgi.00084.2009.—Splanchnic vasodilation is the pathophysiological hallmark in the development of the hyperdynamic circulatory syndrome in liver cirrhosis and portal hypertension. This has been attributed so far mainly to a marked vascular hyporeactivity to endogenous vasoconstrictors. However, myogenic tone and vessel stiffness have not been addressed in mesenteric arteries in liver cirrhosis. CCl4-induced ascitic cirrhotic (LC) and age-matched control rats, portal vein-ligated (PVL) rats, and sham-operated rats were investigated. Third-order mesenteric resistance arteries were studied under no-flow conditions using a pressure myograph measuring media thickness and lumen diameter in response to incremental increases in intramural pressure, from which wall mechanics were calculated. Electron microscopy was used for investigation of wall ultrastructure, especially the fenestrae in internal elastic lamina (IEL). In PVL animals, no significant change in passive vessel strain, stress, media-to-lumen ratio, or cross-sectional area was noted. In contrast, in LC rats, vessel strain was markedly elevated compared with healthy control rats, indicating a marked reduction in vessel stiffness. In addition, the strain-stress curve was shifted to the right, and the elastic modulus in dependency on vessel stress decreased, demonstrating predominantly structure-dependent factors to be involved. The media-to-lumen quotient was not significantly altered, but cross-sectional area was widely increased in LC rats, indicating hypertrophic outward remodeling. These findings were paralleled by enlarged fenestrae in the IEL but no change in thickness of IEL or proportion of extracellular matrix or vascular smooth muscle in LC rats. We concluded that, in long-standing severe portal hypertension such as ascitic LC but not in short-term conditions such as PVL, mesenteric resistance arteries exhibit vascular remodeling and markedly less resistant mechanical properties, leading to decreased vessel stiffness accompanied by structural changes in the IEL. This may well contribute to the maintenance and severity of splanchnic arterial vasodilatation in LC.

mesenteric arteries; vasodilation

In advanced cirrhosis, the circulation is hyperdynamic with decreased systemic vascular resistance and arterial blood pressure and increases in cardiac output and plasma volume (17). This hyperdynamic circulatory syndrome has been shown to contribute essentially to severe complications such as variceal hemorrhage, ascites formation, and hepatorenal syndrome and thus determines mortality in portal hypertensive conditions.

The main site of changes in vascular resistance in this scenario is the splanchnic circulation. In fact, arterial vasodilation is known to occur earliest and most pronounced in the mesenteric circulation in portal hypertension, rendering splanchnic vasodilation as the pathophysiological hallmark in the development of the hyperdynamic circulation (44). This marked reduction in mesenteric resistance has so far been attributed to diminished vascular reactivity to endogenous vasoconstrictors via enhanced release of vasodilators and defects in contractile pathways of vascular smooth muscle cells (19).

Structural changes in arterial vessels may as well contribute to the vascular dysfunction in portal hypertension. Increases in central arterial compliance have been shown to be increased in cirrhotic patients (20, 21). Moreover, changes in arterial wall thickness, cross-sectional area, and lumen diameter have been demonstrated in aortic vessels of cirrhotic rats (14). However, none of these investigations did evaluate specifically the passive mechanical properties of mesenteric resistance vessels, which are known to be of fundamental importance for the function of the circulation. In resistance vessels, the pressure-dependent caliber of individual segments at full dilation sets the limit for organ perfusion. Moreover, also in presence of vasoactive mediators, a clear relation exists between the diameter where active force is maximal and the passive diameter (39). In addition, arterial compliance depends on the properties of arterial intrinsic elastic characteristics. Vascular remodeling is a well-known phenomenon occurring in response to changes in transmural pressure and blood flow. In fact, chronic modifications in blood flow cause adaptive changes in the structure and elasticity of the vessels. This remodeling is characterized by a change in the pressure diameter and stress-strain relation under passive nonflow conditions (29). Moreover, our understanding of the pathological mechanisms leading to this remodeling is still incomplete. It has been shown that resistance arteries display abnormal elastic fiber content and organization in stroke-prone spontaneously hypertensive rats (4, 5). These alterations are associated with vascular stiffening. We hypothesize that, in a hypotensive state like in liver cirrhosis (LC), less vascular stiffness could be influenced by elastin structure as well. To the best of our knowledge, there are no studies on elastin organization in resistance arteries in LC.

Therefore, we aimed to investigate the passive static mechanical properties of mesenteric small arteries during experimental portal hypertension. CCl4-induced cirrhosis with ascites was used as a model of long-standing severe portal hypertension. The model of portal vein ligation (PVL) was applied to simulate short-term portal hypertension.

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MATERIALS AND METHODS

Animal Models

All experimental procedures in this study were conducted according to the German Physiological Society principles for the care and use of laboratory animals (Granted permission number 621-2531.1-16/03, Government of Oberpfalz, Bavaria).

Sodium nitroprusside (SNP) were added after preconstriction with NE 10⁵ M. Only preparations sensitive to NE 10⁻⁵ M were included in the study. Three points along the vessel with use of a calibrated video system were reached to allow the vessel to reach a steady-state diameter. The video system was calibrated with known dimension vessels. A ligature (silk gut 3–0) was placed around a 20-gauge blunt-tipped needle lying alongside the portal vein. Subsequent removal of the needle yielded a calibrated stenosis of the portal vein. In sham-operated rats (n = 7), the same operation was performed with the exception that, after isolating the portal vein, no ligature was placed. After the operation, the animals were housed in plastic cages and allowed free access to standard rat chow. All studies were performed in 12–18-h fasted animals 10–14 days after surgery.

Preparation. Rats were killed by cervical dislocation. The intestines were exposed by a median incision of the abdomen, and one segment of jejunum together with the mesenteric bed was quickly excised and placed in a dissection dish containing cold physiological salt solution. A 2–3-mm-long segment of 3 rd order branch of the superior mesenteric artery was carefully cleared from surrounding adipose tissue. After dissection, the artery was transferred to the chamber of a pressure myograph (Danish Myo Technology, Aarhus, Denmark) for cannulation. Suffusion and perfusion were performed using oxygenated 37°C Krebs solution (95% O₂, 5% CO₂) containing (in mmol/L): 118 NaCl, 4.7 KCl, 1.2 KH₂PO₄, 1.2 MgSO₄, 2.5 CaCl₂, 25 NaHCO₃, 0.026 disodium EDTA, and 11.0 glucose, pH 7.4. The vessel was mounted on two pipettes and secured with suture. The axial length of the vessel was adjusted by moving one cannula until the vessel walls were parallel without stretch. Vessels were equilibrated under a constant intraluminal pressure (45 mmHg) for 1 h.

Experimental protocol. Experiments were performed under no-flow conditions. Vascular reactivity was tested with norepinephrine (NE) (10⁻⁵ M). Endothelial function was pretested with ACh (10⁻⁴ M). Afterward, the function of arteriolar smooth muscle and endothelium was assessed with cumulative doses of ACh (10⁻⁷–10⁻⁴ M) and sodium nitroprusside (SNP) (10⁻⁵–10⁻³ M) known to be endothelium-dependent and -independent dilatory agents, respectively. ACh and SNP were added after preconstriction with NE 10⁻⁵ M. Only preparations with >50% NE-induced vasoconstriction were used. Intravascular pressure was decreased to 3 mmHg after a wash-out period of 30 min, allowing the vessels to equilibrate. For assessment of passive mechanical properties, vessels were deactivated of myogenic tone by perfusion with Ca²⁺-free Krebs solution containing EDTA 10 mmol/l for 30 min. Then intravascular pressure was increased to 10, 20, 30, and 40 mmHg and afterward in 20-mmHg steps until 140 mmHg. The pressure was maintained at each pressure step until stable conditions were reached to allow the vessel to reach a steady-state diameter. The changes in internal diameter as well as media thickness of vessels in response to each increase in intravascular pressure were measured at three points along the vessel with use of a calibrated video system (Danish Myo Technology).

Calculation of Morphology and Mechanics

Media CSA was obtained by subtraction of the internal CSA from external CSA with the following equation: CSA = [(π/4)(dₑ² - dᵢ²)], where dₑ and dᵢ were external and internal (lumen) diameters, respectively. Furthermore, media-to-lumen ratio (MLR), representing geometric characteristics of vessels studied, was calculated by wall thickness (of media) divided by internal (lumen) diameter. Growth index (GI) was calculated as GI = 100 × [(CSAᵢ - CSAₑ)/CSAᵢ] where CSAᵢ and CSAₑ are the CSAs of cirrhotic or healthy control vessels, respectively (18).

Circumferential stress, which corresponds to wall tension or distending force on the vessel wall, was calculated as σ = (Pa/dₘ), where P was intraluminal pressure, and dₑ and dₘ were lumen diameter and media thickness, respectively. Circumferential strain, which corresponds to pressure-induced relative increases in lumen diameter, was calculated as ε = (dₑ - d₀)/d₀, where d₀ was the observed lumen diameter at a given intraluminal pressure and dₑ was the original diameter measured at 3 mmHg, respectively. Elastic modulus describes the intrinsic elastic properties of the wall material. It was obtained by fitting stress-strain data from each vessel to an exponential curve (y = aeᵇₓ): σ = σ₀eᵇε, where σ₀ was the stress at the original diameter and β was a constant related to the rate of increase of the stress-strain curve.

Ultrastructure of Rat Mesenteric Arteries

Small tissue samples (~1 mm³) were routinely fixed in 0.1 M cacodylate-buffered Karnovsky solution (2.5% glutaraldehyde and 1% paraformaldehyde; overnight, room temperature), postfixed in 1% osmium tetroxide (2 h) at pH 7.3, dehydrated in graded ethanol, and embedded in the EmBed-812 epoxy resin (all reagents from Science Services, Munich, Germany). After 48-h heat polymerization at 60°C, semithin (0.8 µm) sections were cut and stained with toluidine blue/basic fuchsin, and, after selection of appropriate areas of interest, the resin block was trimmed for ultrathin sectioning. Ultrathin (80 nm) sections were cut with a diamond knife on a Reichert Ultracut-S ultramicrotome (Leica, Vienna, Austria) and double contrasted with aqueous 2% uranyl acetate and lead citrate solutions for 10 min each. The sections were examined with a LEO912AB electron microscope (Zeiss, Oberkochen, Germany) operating at 80 kV in zero-loss mode; the images were documented (TIFF-format, calibrated for distance measurements) with a side-entry mounted 1,000 × 1,000 pixel digital camera.

Quantitative analysis was performed with Metamorph Image analysis software (Universal Imaging, Downingtown, PA) from electron microscopical projections of serial images of sections of the vessel wall. In the projections of the internal elastic lamina (IEL), the following parameters were measured: length of fenestræ, mean IEL thickness (area occupied by IEL divided by length of IEL in the according section), and proportion of vessel wall occupied by extracellular matrix or vascular smooth muscle. For evaluation of extracellular matrix and vascular smooth muscle, we used a magnification of ×1,250. For investigation of length of fenestræ and IEL thickness, a magnification of ×3,150 was used. Study of the content and organization of elastin was performed in mesenteric resistance arteries of LC and control rats (n = 3, each) in two vessels in each case.

Statistics

Data are presented as means ± SE. Differences were considered statistically significant at P < 0.05 and were determined with ANOVA for repeated measurements and unpaired Student’s t-test, as appropriate. The strain-stress relation was fitted to an exponential curve for each vessel, and the slope for each curve was determined. Similarly the stress-elastic modulus relation was fitted to a regression line for each vessel, and the slope for each curve was determined. The slopes were compared between groups using unpaired Student’s t-test.
RESULTS

Baseline Characteristics

All CCl₄-treated animals used presented with ascites and showed macroscopic micronodular LC. No differences in body weight between LC and control rats, as well as PVL and sham rats, were observed.

Maximal vascular response to NE tended to be reduced in LC (69 ± 4% vs. 75 ± 2%) and PVL rats (60 ± 4% vs. 69 ± 3%) compared with control and sham rats, respectively. This confirms multiple independent previous investigations demonstrating vascular mesenteric hyporesponsiveness during experimental portal hypertension.

Passive Vessel Morphology

In vessels from ascitic LC rats, lumen was greater and media thickness slightly but nonsignificantly increased compared with age-matched healthy controls (Fig. 1, B and D). There-

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Fig. 1. Morphology of small mesenteric arteries in experimental portal hypertension. Left: data obtained in portal vein ligation (PVL) and sham animals. Right: experiments in cirrhotic (LC) and control (CTR) rats. Internal diameter (lumen) (A and B), media thickness (C and D), media-to-lumen-ratio, and media cross-sectional area (CSA) at 45 mmHg, respectively (E and F). *P < 0.05 vs. control rats.

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fore, a slightly reduced (not significant) MLR but vastly enhanced media CSA was found in LC rats (Fig. 1F). In contrast, PVL rats presented with no significant change in lumen, external diameter, media thickness, MLR, and CSA (Fig. 1, A, C, and E). The GI was found to be higher in LC rats compared with PVL animals (25 vs. 9%).

**Vascular Mechanics**

*Isobaric evaluation*. The capacity for maximal passive dilation was unaltered in PVL rats compared with sham animals but was markedly enhanced in mesenteric arteries from ascitic LC rats as shown by a significant upward shift of the intraluminal pressure-lumen diameter curve compared with control rats (Fig. 1, A and B). Moreover, the relative increase in lumen diameter (strain) and media stress in response to increments of pressure was unchanged in PVL rats (Fig. 2, A and C). In contrast, isobaric circumferential strain development was found to be significantly increased in ascitic LC rats compared with control rats (Fig. 2B). Because strain is the lumen increase in relation to the basic lumen diameter, this measure of elasticity is independent of the observed differences in baseline diameter. Isobaric circumferential stress tended to increase more in response to pressure increases in LC animals; however, this did reach statistical significance only for the three highest pressures applied (Fig. 2D). Isobaric vessel stiffness, namely the relationship of incremental elastic modulus ($E_{inc}$) to intraluminal pressure, was found unaltered in ascitic LC rats and PVL rats compared with corresponding control groups (Fig. 2, E and F).

*Geometry-independent evaluation*. The relationship between circumferential strain and media stress was identical in PVL and sham rats but markedly shifted to the right in ascitic LC rats (Fig. 3, A and B). The slope of the curve was significantly steeper in control rats ($6.70 \pm 0.30$ vs. $5.25 \pm 0.22; P < 0.05$). This clearly reflects a marked change in geometry-independent vessel stiffness. Moreover, the relationship of $E_{inc}$ to media stress was once more unchanged in PVL animals but significantly decreased in ascitic LC rats compared with control animals (Fig. 3, C and D), with significantly lower slope of the regression line ($5.85 \pm 0.28$ vs. $7.79 \pm 0.53; P < 0.05$).

**Ultrastructure of mesenteric arteries**. Electron microscopy of IEL structure enables quantitative evaluation of fenestration of the IEL visualized in LC and control rats. In LC rats, size of fenestrae were increased compared with control rats (Fig. 4A) even if statistical significance was missed because of low numbers of animals studied. In contrast, no change in thickness of IEL was observed in LC rats compared with controls (Fig. 4B). Moreover, evaluation of vessel wall composition revealed no change in relative proportion of extracellular matrix and of vascular smooth muscle in mesenteric arteries of LC rats compared with controls (Fig. 4, C and D).

**DISCUSSION**

Structural alterations of small arteries may compromise a combination of growth and remodeling (18). Here we show that cirrhotic mesenteric small arteries show a clear growth component (GI 25%). Moreover, hypertrophic remodeling can be assumed as being characterized by increased lumen and external diameter with markedly enhanced CSA. This is in accordance with the well-known phenomenon that vascular structure continuously adapts to local pressure and flow (9, 24). Thus increasing flow in general is known to induce outward remodeling in large (36) and small arteries (38). Moreover, chronic increases in flow are accompanied by wall hypertrophy aiming to normalize circumferential wall stress that increases during expansion of the vessels (32). Such structural adaptation in response to hyperperfusion has been reported in mesenteric resistance arteries in diabetes (8) and pregnancy (25). In advanced cirrhosis, excessive increases in mesenteric blood flow are known to be present and are thought to constitute the primary event in the so-called “peripheral arterial vasodilation” hypothesis. Therefore, the observed eccentric nature of mesenteric arterial growth during long-standing portal hypertension seems to represent a logical adaptation to this high-flow condition in the splanchnic circulation. Indeed, angiogenesis has been demonstrated to be increased in the splanchnic vasculature in portal hypertensive rats, contributing largely to the development and severity of the splanchnic hyperdynamic circulation (12, 35, 37).

Changes in wall mechanics (stiffness) of resistance arteries influence pressure-diameter relationships of blood vessels. The approach chosen in this investigation completely abrogates possible effects of flow-related changes in vascular diameter and/or flow-induced release of vasoactive mediators. Thereby, we could show that the morphometric modifications described effectively increase isobaric wall stress in small mesenteric arteries of LC but not PVL rats. Vessels from LC rats but not PVL animals passively dilate more and respond with greater increases in internal diameter in response to incremental increases in luminal pressure compared with corresponding control rats. Such a decrease in arterial stiffness can be separated in a geometry-dependent and –independent component (30). Because the relationship between elastic modulus and intraluminal pressure was not altered in vessels from LC rats, isobaric, geometry-dependent stiffness seems to be not importantly affected. In contrast, the incremental elastic modulus in relation to wall stress was significantly lower in vessels from LC rats. Moreover, the strain-stress relationship was markedly shifted to the right in LC animals. This clearly indicates changes in the stiffness of wall components, which is determined by the relative proportions, content, and arrangement of elastin and collagen (3). However, the structural response of the small arteries in LC animals was apparently insufficient to normalize circumferential wall stress. Such elevation in wall stress therefore can be deleterious for the functional integrity of the vascular wall (16) and may contribute to enhanced permeability of splanchnic blood vessels in portal hypertension (15).

The observed increase in overall elasticity in mesenteric resistance arterioles in ascitic LC rats may well contribute to splanchnic vasodilation independent of any vascular hyporeactivity to vasoconstrictors and/or defects in vascular smooth muscle signaling. At any given vessel diameter, mesenteric arterioles of LC rats presumably require a greater active vasoconstrictive input to achieve similar vascular tone and pressure compared with control vessels. Indeed, at isometric smooth muscle contraction, elastic modulus of rat mesenteric resistance vessels increases up to 30 times (41), greatly increasing vasoconstrictive capacity of the vessel. It is tempting to speculate that the observed lack of vessel stiffness under passive conditions translates into defects in dynamic elasticity under conditions of enhanced vasoconstrictors. Moreover, this in-
crease in vascular distensibility may, especially in areas with marked enhancement in shear stress, contribute to the development of arteriovenous communications (40). Finally, increased elasticity affects blood-flow velocity and shear stress because altered mechanics of the vascular wall can affect the velocity of pulse wave, wave reflection, and pulsatility of vessels. The clinical relevance of these findings, however, remains to be established.

Arterial compliance has been reported to be increased in cirrhotic patients before (20, 21). However, these whole body measurements and estimates of particularly central arterial compliance do not reflect arterial elasticity at vessels smaller than 1 mm (34). Nonetheless, the degree of increase in arterial compliance has been shown to be related to the severity of the hyperdynamic circulation (21). In fact, the strong coupling observed between arterial compliance and the decrease in
systemic vascular resistance in cirrhotic patients, remaining even after manipulation of both variables, suggests a common genesis of arteriolar dilatation and altered wall characteristics of the arterial tree in cirrhosis (20). This is well in accordance with our data and the observation that LC rats with ascites present with a more severe state of hyperdynamic circulation compared with PVL rats (27). In addition, the duration of chronic increases in mesenteric blood flow is only about 1 wk in PVL rats compared with several weeks in ascitic LC rats (2). Therefore, mesenteric resistance vessels of ascitic LC rats face higher flow for a vastly longer period of time compared with vessels of PVL rats. In addition, LC in the decompensated state is characterized by more severe bacterial translocation and associated portal-venous inflow of gut-derived bacterial products and release of proinflammatory cytokines (42) known to modulate vascular responses. These factors may represent possible explanations for the observed adaptation of vessel structure and elasticity in ascitic LC but not PVL rats.

However, the exact mechanisms of hypertrophic outward remodeling and increases in structure-dependent elasticity accompanying longstanding hyperperfusion are not yet completely elucidated but may involve an upregulation of growth factor genes and/or genes involved in collagen and elastin turnover or arrangement (26, 28). In fact, enhanced expression of VEGF and PDGF has been evidenced in the intestinal microcirculation during portal hypertension (1, 12, 27). In addition, impaired collagen degradation has been reported to occur in aortas of LC rats, leading to enhanced collagen IV accumulation (13). However, we failed to observe any change in proportion of extracellular matrix occupying vessel wall area in resistance arteries of LC rats. This discrepancy may well be due to the difference in vessel type and size being studied.

Nonetheless, despite a lack of change in quantity of elastin, an increase in size of fenestrae of the IEL was noted in resistance arteries of LC compared with control rats. In fact, the present study provides the first in situ visualization of fenestrations of the IEL in LC rats even if we have to state that we were only able to measure the diameter of the fenestrae at the given section and not the total area occupied by the fenestrae. Elastin is mainly present in the IEL (6, 10), and its fenestrae are a crucial determinant of mechanical properties in resistance arteries. In spontaneously hypertensive rats, it has been shown that inward remodeling is associated with abnormal elastic fiber organization, leading to smaller fenestrae in the IEL (4, 7) and stiffer arteries. The organization of elastin in the remodeled vascular wall of LC rats is still unclear. However, we propose that qualitative changes in the elastic lamina structure leading to enlarged fenestrae may have occurred and
Fig. 4. Characteristics of internal elastic lamina (IEL) in small mesenteric arteries of cirrhotic and control rats as assessed by electron microscopy. Shown here are size of fenestrae in the IEL (A), average thickness of the IEL (B), percentage of area of extracellular matrix (EM) (C), percentage of area of vascular smooth muscle cells (VSMC) (D), representative electron microscopical image of fenestrae (white bar) of IEL in LC rats (original magnification ×3,150) (E), and exemplaric electron microscopical image of fenestrae (white bar) of IEL in CTR rats (original magnification ×3,150) (F).
that these changes may, at least in part, be responsible for the mechanical adaptation of the vascular wall in LC rats. Considering that such changes represent largely fixed morphometric changes being most likely irreversible, it is tempting to speculate that this, at least in part, explains the lack of normalization in splanchnic hemodynamics after liver transplantation (31). Finally, this is in accordance with a study of Somoza et al. (33), in which liver growth factor, a mitogen for liver cells that reduces fibrosis in a rat model of cirrhosis (11), enlarged the area occupied by fenestrae in the IEL of carotid arteries from spontaneously hypertensive rats (33). Therefore, the data presented here suggest that the observed decrease in mesenteric resistance artery stiffness in LC rats, at least partly, may be attributable to an increased size of fenestrae of IEL.

In addition, vascular nitric oxide (NO) release has been shown to augment arterial elasticity in human arteries (23) and is well known to be overproduced in portal hypertension (44). In fact, vascular overproduction has been demonstrated to be more pronounced in the mesenteric circulation of ascitic LC rats compared with PVL rats (27). Finally, chronic NO inhibition normalizes extracellular matrix turnover in aortae of LC rats (13), indicating a key role for NO in the observed vascular remodeling. However, the regulation of arterial compliance is complex and greatly differs between aorta, large arteries, and particularly resistance vessels (22) and thus remains to be determined for mesenteric arterioles of ascitic LC rats.

In summary, in ascitic LC, structural changes of mesenteric resistance arteries representing hypertrophic outward remodeling occur and increase wall stress. Moreover, these animals exhibit a markedly decreased isometric mesenteric stiffness, demonstrating additional hemodynamically potent geometry-independent increases in elasticity, which may be attributable, at least partly, to an enlargement of fenestrae in the IEL. In contrast, PVL rats present with normal mesenteric morphometry and unchanged distensibility. This suggests that, in longstanding and severe hyperdynamic conditions such as LC with ascites but not in short-term portal hypertension, mesenteric resistance arterioles become remodeled, leading to less resistance-mechanical properties. This may contribute to maintenance or further exacerbation of the circulatory dysfunction present in advanced LC.

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