Perfusion Patterns of Peripheral Pulmonary Lesions in COVID-19 Patients Using Contrast-Enhanced Ultrasound (CEUS)

A Case Series

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Purpose—To describe perfusion patterns of peripheral pulmonary lesions (PPLs) in COVID-19 patients using contrast-enhanced ultrasound (CEUS).

Patients and methods—From April 2020 until July 2020, 11 consecutive patients with RT-PCR-confirmed COVID-19 and PPLs sized over 5 mm were investigated by B-mode ultrasound (B-US) and CEUS. The homogeneity of enhancement (homogeneous and inhomogeneous) was examined retrospectively using CEUS. An inhomogeneous enhancement was defined as a perfused lesion with coexisting non-perfused areas (NPA).

Results—On B-US, all 11 patients showed an interstitial syndrome (B-lines) with PPLs between 0.5 and 6 cm. On CEUS, all cases showed peripheral NPA during the complete CEUS examination. One patient underwent a partial lung resection with subsequent histopathological examination. The histological examination showed vasculitis, microthrombus in the alveolar capillary, and small obliterated vessels.

Conclusion—In our case series, PPLs in patients with RT-PCR-confirmed COVID-19 infection presented a CEUS pattern with NPA during the complete CEUS examination. Our findings suggest a peripheral pulmonary perfusion disturbance in patients with COVID-19 infection. In 1 case, the histopathological correlation with the perfusion disturbance in the PPL was proven.

Key Words—CEUS; COVID-19; histopathological correlation; peripheral pulmonary perfusion disturbance; SARS-CoV-2; ultrasound

Introduction

The lung has a dual blood supply via a pulmonary artery with high capacity and low resistance and a bronchial artery with low capacity and high resistance. In some pathological conditions, such as bronchial carcinomas and bronchiectasis, the bronchial circulation is increased, and the blood supply is predominantly via the bronchial arteries. The reason for this is the bronchial circulation’s high angiogenic capacity compared with that of the pulmonary circulation.
This knowledge provided the motivation to examine the type-specific blood-flow patterns in different lung lesions with different imaging methods, including ultrasound.4–11 Görg et al demonstrated that, in color Doppler sonography mapping, a pulmonary-arterial supply in peripheral pulmonary lesions (PPLs) can be differentiated from a bronchial-arterial supply by a specific pattern and described this specific pattern in different lung lesions.4 Since the development of contrast-enhanced ultrasound (CEUS), this has also been used to study the perfusion patterns of peripheral pleural and pulmonary lesions, as a safe and noninvasive method.5,7 With CEUS, different perfusion patterns in different entities were observed in peripheral pleural and pulmonary lesions.5,7 Moreover, several studies have continued to demonstrate the significance of CEUS for various diseases such as pneumonia, atelectasis, infectious pleurisy, bronchial carcinoma, and lung infarction.5,7–11 Furthermore, CEUS was recommended as an imaging modality in 2018 in the EFSUMB guidelines for non-hepatic organs for the investigation of pleural-based lung lesions and in particular for the characterization of peripheral pulmonary infarction in pulmonary arterial embolic disease.12 The diagnostic value of CEUS for the characterization of the PPLs in suspected pulmonary arterial embolic disease has recently been proved in several studies.8–10 CEUS can demonstrate a lack of enhancement or inhomogeneous enhancement during the complete CEUS examination.8–10 Histologic examination of the lesions confirmed pulmonary infarction in patients with pulmonary arterial embolic disease.10 Patterns of inhomogeneous enhancement with non-perfused areas (NPA) due to necrosis and abscess formation were seen using CEUS in chronic pneumonia, obstructive atelectasis, and peripheral lung cancer.5,7,11 However, in these causes of consolidation, the lack of enhancement or inhomogeneous enhancement was usually localized in central areas.7

The coronavirus (SARS-CoV-2) pandemic, which has been spreading since December 2019, caused a global health crisis, requiring unprecedented measures to manage it.13 In patients with the novel coronavirus (SARS-CoV-2), systemic microcirculatory disturbances and increased thromboembolic events have been reported.14,15 The cause of the microcirculatory disturbance could be endothelial cell damage and associated fibrinous thrombi in small vessels, which have already been described in several autopsy reports.14–16 Although thromboembolic events may also be found in patients with severe influenza virus infection and are not specific to COVID-19, alveolar

Table 1. Demographic and Clinical Data for the 11 Patients in the Study

| Patient Number | Sex | Age | Comorbidity | ICU Admission | Histological Examination of the Lung Tissue |
|----------------|-----|-----|-------------|--------------|-------------------------------------------|
| 1              | m   | 79  | No known comorbidity in the medical history | +            | −                                         |
| 2              | m   | 23  | Spastic tetraplegia and cerebral shunts due to myelomeningocele | +            | −                                         |
| 3              | m   | 52  | Glioblastoma WHO IV | −            | −                                         |
| 4              | m   | 39  | Arterial hypertension and active hepatitis B | −            | +                                         |
| 5              | m   | 73  | Arterial hypertension, chronic kidney disease, and chronic lymphocytic leukemia | −            | −                                         |
| 6              | f   | 62  | Rheumatoid arthritis | −            | −                                         |
| 7              | m   | 70  | Arterial hypertension, diabetes mellitus, chronic kidney disease in post-kidney transplant status, hyperlipidemia, and first-degree atrioventricular block | +            | −                                         |
| 8              | m   | 54  | Arterial hypertension, diabetes mellitus, and heart failure | −            | −                                         |
| 9              | m   | 85  | Arterial hypertension, atrial fibrillation, and cerebral infarction | +            | −                                         |
| 10             | m   | 65  | No known comorbidity in the medical history | +            | −                                         |
| 11             | m   | 54  | Arterial hypertension, hyperlipidemia, and adiposity | +            | −                                         |

Abbreviations: f, female; ICU, intensive care unit; m, male.
Capillary microthrombi were found to be 9 times as prevalent in patients with Covid-19 as in patients with influenza.\textsuperscript{15} The injuries in the endothelium are assumed to be caused by a direct viral infection or an immune response of the host.\textsuperscript{14} The immunological character of COVID-19 infection has been reported

**Figure 1.** Histologic changes in the lung of patient #4 show vasculitis, microthrombi, and subsequent obliteration of small vessels. (A) and (B) Perivascular lymphocytic infiltrate (*), indicating vasculitis, with interposed several-day-old bleeding residues (arrows), implying previous vascular damage. Panel (B) is a higher magnification of panel (A). Arrowheads demark endothelial lining, also infiltrated by leucocytes. (C) Microthrombus in alveolar capillary (square). (D) Smaller obliterated vessels (rhombus), presumably after vasculitis or thrombosis. Scale bar: 100 \( \mu m \), respectively.

**Table 2.** Laboratory Data for the 11 Patients in the Study

| Laboratory Values | D-dimer (mg/L FEU) | C-reactive Protein (mg/L) | Ferritin (\( \mu g/L \)) | Interleukin-2 receptor (kU/L) | Interleukin-6 (pg/ml) | TNF-\( \alpha \) (ng/L) |
|-------------------|-------------------|--------------------------|------------------------|-----------------------------|----------------------|---------------------|
| Normal range      | 0–0.5             | <5                       | 30–400                 | 230–920                     | <7                   | <8.1                |
| Pt. 1             | 33.10 \( \uparrow \) | 246.8 \( \uparrow \)     | 146911                 | 3234 \( \uparrow \)         | 496 \( \uparrow \)    | 13.9 \( \uparrow \)  |
| Pt. 2             | 2.76 \( \uparrow \) | 221.1 \( \uparrow \)     | 415 \( \uparrow \)     | 616 \( \uparrow \)          | 104 \( \uparrow \)    | <4 \( \uparrow \)    |
| Pt. 3             | 3.72 \( \uparrow \) | 41.5 \( \uparrow \)      | 118                    | 793 \( \uparrow \)          | 28 \( \uparrow \)     | 11.6 \( \uparrow \)  |
| Pt. 4             | 2.34 \( \uparrow \) | 60.6 \( \uparrow \)      | 233                    | 1003 \( \uparrow \)         | 26 \( \uparrow \)     | 11.1 \( \uparrow \)  |
| Pt. 5             | 0.98 \( \uparrow \) | 53.2 \( \uparrow \)      | 3371                   | 1967 \( \uparrow \)         | 157 \( \uparrow \)    | <5 \( \uparrow \)    |
| Pt. 6             | 0.72 \( \uparrow \) | 35.5 \( \uparrow \)      | 673                    | 1402 \( \uparrow \)         | 8 \( \uparrow \)      | 10.6 \( \uparrow \)  |
| Pt. 7             | 17.63 \( \uparrow \) | 5.0 \( \uparrow \)      | 285                    | 417 \( \uparrow \)          | 6 \( \uparrow \)      | 12.0 \( \uparrow \)  |
| Pt. 8             | 0.86 \( \uparrow \) | 7.8 \( \uparrow \)       | 611 \( \uparrow \)     | 2711 \( \uparrow \)         | 8 \( \uparrow \)      | 278 \( \uparrow \)  |
| Pt. 9             | 0.82 \( \uparrow \) | 55 \( \uparrow \)        | 230                    | 642 \( \uparrow \)          | 36 \( \uparrow \)     | 5.8 \( \uparrow \)   |
| Pt. 10            | 1.21 \( \uparrow \) | 93.0 \( \uparrow \)      | 642                    | 1892 \( \uparrow \)         | 41 \( \uparrow \)     | 13.3 \( \uparrow \)  |
| Pt. 11            | 0.87 \( \uparrow \) | 63.9 \( \uparrow \)      | 1334                   | 889 \( \uparrow \)          | 31 \( \uparrow \)     | 11.4 \( \uparrow \)  |

Abbreviations: FEU, fibrinogen equivalent units; kU/L, kilo unit per liter; mg/L, milligram per liter; \( \mu g/L \), microgram per liter; ng/L, nanogram per liter; pg/ml, picogram per milliliter; Pt, patient.
recently. It has been observed that an increase in cytokines such as interleukin-2R, interleukin-6, and tumor necrosis factor alpha (TNF-α) correlate with the severity of the disease. In addition, it was shown that the anti-inflammatory drug ruxolitinib (a JAK1/2 kinase inhibitor) reduced inflammatory blood

Table 3. B-US Data for the 11 Patients in the Study

| Patient Number | Ri/Le PE | Ri/Le B-line | Ri/Le Frag | Ri/Le PPLs (size) | Ri/Le Airb |
|---------------|---------|-------------|------------|------------------|----------|
| 1             | −/−     | +/+         | +/+        | +/+ (0.5 cm)     | −/−      |
| 2             | −/+     | +/+         | −/−        | −/+ (3 cm)       | −/+      |
| 3             | −/−     | +/+         | +/−        | +/− (0.5 cm)     | −/−      |
| 4             | −/−     | +/+         | +/+        | +/+ (0.5 cm)     | −/−      |
| 5             | −/−     | +/+         | −/+        | −/+ (2 cm)       | −/+      |
| 6             | −/−     | +/+         | −/+        | −/+ (3 cm)       | −/+      |
| 7             | −/+     | +/+         | +/+        | +/+ (6 cm)       | −/+      |
| 8             | +/+     | +/+         | −/+        | −/+ (4 cm)       | −/+      |
| 9             | −/+     | +/+         | −/+        | −/+ (6 cm)       | −/+      |
| 10            | −/+     | +/+         | −/+        | +/+ (4 cm)       | −/+      |
| 11            | −/+     | +/+         | −/+        | −/+ (2 cm)       | −/+      |

Abbreviations: Airb, air bronchogram; Frag, fragmented pleura; Le, left side; PE, pleural effusion; PPLs, peripheral pulmonary lesions; Ri, right side.

Figure 2. A 24-year-old male patient with RT-PCR-confirmed COVID-19. (A) B-US shows a small amount of effusion, with inhomogeneous lung consolidation. (B) CEUS after 5 seconds shows a pulmonary arterial enhancement, with small peripheral non-perfused areas (NPA) (*). (C) Higher magnification of the area marked by a red rectangle in panel (B). Arrowheads demark the non-perfused area during the complete CEUS examination. (D) Graphical illustration of panel (C).
cytokine levels and improved respiratory symptoms in a case of acute respiratory distress syndrome induced by COVID-19.18

Thromboembolic events in patients with COVID-19 infection identified using computed tomography pulmonary angiography (CTPA) have been correlated with histopathological data.19,20 Interestingly, using CTPA, the pulmonary embolism was observed more in peripheral lung segments.18 In most cases, pulmonary embolism is associated with an hemorrhagic infarction in patients with COVID-19 infection, which could make an examination of the perfusion pattern of embolic lesions with CEUS possible.10,21 A recent study has demonstrated the diagnostic importance of CEUS for the detection of microcirculatory disorders in patients with COVID-19 infection.22

The aim of this study is to describe perfusion patterns of PPLs in patients with COVID-19 using CEUS and to provide a description of the histopathological correlation in 1 case from the study.

Patients and Methods

From April 2020 until May 2020, 11 patients with reverse transcription polymerase chain reaction (RT-PCR) confirmed COVID-19 and PPLs over 5 mm were investigated by B-mode ultrasound (B-US) and CEUS. The lesion with the largest non-perfused area was chosen as the reference lesion. None of the patients had contraindications for CEUS examination with SonoVue, including hypersensitivity to the ultrasound contrast medium, known right-to-left shunts, severe pulmonary hypertension, or adult respiratory distress syndrome (ARDS) according to the HOROWITZ index.23 This study was approved by the local

Figure 3. A 54-year-old male patient with RT-PCR-confirmed COVID-19. (A) B-US shows a small amount of effusion, with homogeneous peripheral lung consolidation. (B) CEUS after 21 seconds shows a bronchial arterial enhancement at the edge, with complete non-enhancement of the lesion (*). (C) Higher magnification of the area is marked by a red rectangle in panel (B). Arrowheads demark the non-perfused area during the complete CEUS examination. (D) Graphical illustration of panel (C).
ethics committee and conducted in accordance with the amended Declaration of Helsinki and informed consent was obtained from each patient for ultrasound examinations.

The ultrasound examination was performed with an ACUSON SEQUOIA 512 GI Siemens ultrasound machine according to the standardized lung ultrasound (LUS) protocol of DEGUM for COVID-19 patients. A 4C1 curved array transducer and a frequency of 4 MHz were used for the B-US investigation.

PPLs detected on B-US were subsequently examined using CEUS. The CEUS investigations were performed with the same transducer in 1.5 MHz contrast-specific mode according to the EFSUMB guidelines. A bolus injection of 2.4 ml of SonoVue® (Bracco Imaging S.p.A, Milan) contrast medium was administered via a peripheral venous access, followed by 10 ml NaCl 0.9%, and the lesions were continuously examined for the first 30 seconds. Examination was then repeated every minute intervals up to 5 minutes. The pathological perfusion patterns of the lesions were saved as an image. The following B-US data and CEUS parameters were retrospectively analyzed.

**B-mode ultrasound**
1. The presence of B-lines, fragmented visceral pleura, and PPLs. The PPLs were, by definition, always >5 mm in diameter. These consolidations show either with a homogeneous hypoechoic echo pattern or with an air bronchogram
2. The presence of pleural effusion.
3. The size of the PPLs (in cm).

**CEUS**

The homogeneity of enhancement (HE) is defined in CEUS as homogeneous enhancement versus inhomogeneous enhancement of the PPLs. An inhomogeneous enhancement was defined as a perfused lesion with coexisting peripheral pleural-based NPA. Due to the long and homogeneous enhancement in CEUS, splenic tissue was used as an in vivo reference in the assessment of HE.

The B-US and CEUS data were evaluated retrospectively by 2 independent, experienced investigators (E. S. and C. G.). In the event of discrepancies, the final decision was made by a third experienced investigator (C. T.).

**Results**

**Demographic and Clinical Data**

Of the 11 participants, 10 patients were male, and 1 was female. The mean age of the patients was 59.6 years (range 23–85 years), and 6/11 patients were older than 60 years. In their medical history, 9/11 patients had comorbidities (Table 1).

Six of the 11 patients were admitted to the intensive care unit (ICU). One patient underwent partial lung resection due to secondary abscess 9 days after the sonographic examination. Histopathological analysis of resected lung tissue was performed in the local pathological institute. Histologically, vasculitis, microthrombi, and subsequent obliteration of small vessels were identified (Figure 1). The patients’ demographic and clinical data are presented in Table 1.

**Laboratory Data**

Coagulation (D-dimer) and inflammation parameters (C-reactive protein, ferritin, Interleukin-6, Interleukin-2 receptor, and TNF-α) were measured in all patients. Table 2 shows the laboratory parameters evaluated.

**Imaging Data**

All the patients underwent a low-dose computerized tomography (CT) scan according to the recommendation of the German Society for Radiology. In 3 patients, a CTPA was additionally performed. In 1 of these 3 cases, an acute pulmonary embolism was detected. No acute pulmonary embolism or signs of a perfusion disturbance in lung consolidations were found in the other 2 patients.
All patients were examined with B-US and CEUS. All examiners agreed on the interpretation of the B-US and CEUS data.

**B-mode Ultrasound**

On B-US, all 11 patients showed both-sided interstitial syndrome (B-lines). A total of 7 cases showed a fragmented pleura. The lesions had an average size of 3 cm (range 0.5–6 cm), and PPLs of >1 cm were observed in 8 cases. In 8 cases, PPLs were homogeneously consolidated, and in 3 cases, B-US was accompanied by an air bronchogram. A pleural effusion was seen in 5 patients (Table 3).

**CEUS**

All lesions showed a peripheral inhomogeneous enhancement during the CEUS examination. The size of the peripheral pleural-based NPA was <1 cm in 8 cases (Figure 2) and >1 cm in 3 cases (Figure 3), while 8 cases revealed multiple NPA and 3 cases revealed solitary NPA. Table 4 presents the CEUS data.

**Discussion**

In this study, we investigated the perfusion patterns of PPLs by CEUS in 11 patients hospitalized with COVID-19 pneumonia under standardized conditions. In uncomplicated bacterial pneumonia, CEUS predominantly shows an homogeneous PA enhancement. In some cases, the pneumonic lesions may show a central inhomogeneous enhancement or a central absence of enhancement due to abscess formation or necrosis. In accordance with previous studies, the PPLs in this study all showed a peripheral NPA in the CEUS investigation, which suggests a disturbed perfusion of the lesion. Peripheral inhomogeneous enhancement of a lesion with small NPA or a complete lack of enhancement was observed in PPLs as a consequence of a pulmonary infarction. Microvascular alterations and thromboembolic events in COVID-19 patients have already been reported in several histopathological findings and other imaging methods, such as CTPA. Therefore, the peripheral NPA in PPLs in the CEUS examination could be interpreted as a perfusion disturbance due to inflammatory endothelial injuries. This latter interpretation is supported by the high plasma levels of coagulation (D-dimer) and inflammation parameters (C-reactive protein, ferritin, Interleukin-6, Interleukin-2 receptor, and TNF-α) in our sample.

A low-dose native CT was performed in all patients, in which no information about the perfusion could be obtained. CTPA was additionally performed in 3 of the patients in the study, and only in 1 case was a perfusion disturbance detected. However, it is known that CTPA and CEUS findings do not always correlate. Trenker et al reported that, despite the lack of evidence of a pulmonary embolism with the CTPA, PPLs with a peripheral NPA on the CEUS could indicate a pulmonary infarction. Furthermore, in a follow-up study in 6 patients with perfusion disturbance in CEUS and negative CTPA, a pulmonary infarction was proved by histological validation.

In our study, in 1 of the patients with negative CTPA, a lung resection was performed due to secondary abscess formation, and this was followed by a histopathological examination. Strikingly, the histopathological findings were in accordance with our CEUS results. Histologically, endothelial cell damage, fibrinous thrombi in vessels, and subsequent obliteration of smaller vessels were confirmed. The virus is thought to enter the endothelial cells via the ACE2-receptor, leading to endothelial damage and inflammation throughout different organs in the body. This leads to a vascular barrier breach, followed by tissue edema, consecutive microcirculatory changes, and activation of coagulation with resulting thrombosis. Patients with preexisting endothelial dysfunction, for example, due to diabetes mellitus, obesity, or cardiovascular diseases, carry a higher risk for a serious course of disease.

Despite our small sample, we identified perfusion patterns with evidence of NPA in COVID-19 patients corresponding to the characteristic vessel histopathological findings in COVID-19 patients. However, the pulmonary perfusion disturbances must be regarded as nonspecific, because histologically proven thromboembolic events, such as the correlation with the perfusion disturbance, are also seen in other viral pneumonias, such as severe influenza.

Although these findings could be seen as nonspecific, the identification of NPA in COVID-19 may be important for the clinical course of the disease. In a recent study, the presence of acute pulmonary embolism in CTPA was associated with a severe
clinical course. Furthermore, COVID-19 patients with a severe clinical course were found in postmorte-tem to have a pulmonary thromboembolic event. However, the correlation of our results with the clinical outcome of COVID-19 patients requires further study.

The major limitation of our study is the small sample size. We have examined only 11 patients with CEUS, and all the patients were hospitalized. Furthermore, histological validation was only available for 1 case, and a blind interpretation of the data by the ultrasound examiner was not possible.

In summary, we describe the presence of impaired peripheral perfusion with NPA in PPLs in COVID-19 patients using CEUS. Furthermore, in 1 case, we proved the histopathological correlation with this finding. Further studies are needed to correlate our findings with the clinical course in these patients.

Acknowledgment

The work of Dr. Ehsan Safai Zadeh is funded by part of a research grant from the Anneliese Pohl Foundation (Anneliese Pohl Stiftung). The authors acknowledge this support from the Anneliese Pohl Foundation (Anneliese Pohl Stiftung). Christian Görg received funding from Bracco Imaging. Bracco Imaging supported CEUS workshops at the University Hospital Marburg.

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