BJCR
Brazilian Journal of Case Reports

PCAA
Publicações Científicas de Acesso Aberto

Case Report

The Cardiac pathophysiology of Covid-19

Hubert Daisley [1,*], Oneka Acco [2], Haille Joseph [3], Johann Daisley [4], Martina Daisley [5]

[1] Department of Pathology, San Fernando General Hospital, San Fernando, Trinidad and Tobago, West Indies.
[2] Department of Pathology, The University of the West Indies, Mona, Kingston, Jamaica, West Indies.
[3] Department of Pathology, Scarborough general Hospital, Trinidad and Tobago, West Indies.
[4] Department of Anaesthetic, Scarborough General Hospital, Trinidad and Tobago, West Indies.
[5] Department of Accident and Emergency Medicine, Princess Alexandra Hospital, Anguilla, West Indies.

* Correspondence: profhdjr@gmail.com.

Abstract: The heart is a key target organ in SARS-CoV-2 infection. During the illness stage of acute Covid-19, fibrin thrombi frequently form within the coronary microcirculation, including the vasa vasorum. These thrombi are predominantly located in the abluminal spaces, the sites of pericyte location, of the vessel wall, in both the microvascular and epicardial vessels. A hallmark histopathological finding is the presence of diffuse, focal fibrin deposits surrounding myocardial fibres, which exhibit varying degrees of degeneration and atrophy. This process contributes to myocardial injury, which is reflected both biochemically and clinically in the acute and long-term phases of Covid-19. Myocardial fibrosis results from this pathological cascade, without a concurrent cellular inflammatory response associated with the myocardial stromal fibrin deposits. During the convalescent stage of acute Covid-19, focal myocardial fibrosis and the presence of thrombi within myocardial vessels remain apparent but sparse. Vascular changes, such as fibrin thrombi within the cardiac microcirculation, exhibit similarities to those observed in the pulmonary microcirculation in Covid-19.

Keywords: Severe Covid-19; Illness Stage; Stage of Decline; Coronary microcirculation; Fibrin Thrombi; Pericyte; Abluminal space; Vasa vasorum.

Citation: Daisley H, Acco O, Joseph H, Daisley J, Daisley M. The Cardiac pathophysiology of Covid-19. Brazilian Journal of Case Reports. 2025 Jan-Dec;05 (1):bjcr43.

https://doi.org/10.52600/2763-583X.bjcr.2025.5.1.bjcr43

Received: 31 October 2024
Accepted: 24 November 2024
Published: 27 November 2024

1. Introduction

The microvascular circulation consists of a network of small vessels of the order 2 to 12 micrometres in diameter comprising of arterioles, capillaries, venules and vasa vasorum which exchange oxygen, nutrients, water and waste between blood and tissues. Covid-19 is a disease of microvascular circulation, the pathology of which often results from microvascular thrombosis, affecting multiple organ systems [1-4]. Our observations in two patients who died from severe Covid-19 without medical intervention, confirmed the presence of coronary microvascular and epicardial vessel / vasa vasorum thrombosis.

The detailed postmortem examinations illustrated the cardiac pathology in the illness and decline stages, focusing on how microvascular thrombosis affects myocardial tissues and cardiac function. This observational study provides new insights into the cardiac pathophysiology of acute and long Covid-19, which would impact therapeutics.

2. Case Report

2.1 Patient 1

This was a 65-year-old male who suffered with diabetes mellitus and died at his residence without having any medical intervention. He had a cough, fever and shortness of breath which progressed to difficulty in breathing. He died 10 days after his symptoms began. He was confirmed at postmortem as having Covid-19 with nasopharyngeal swabs

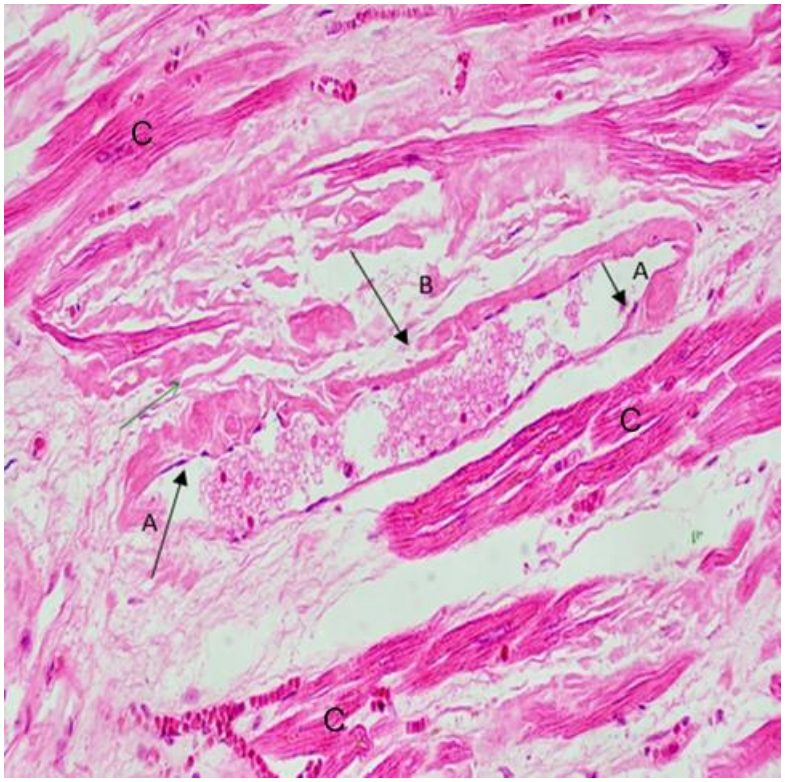
using Abbott Real-time SARS-CoV-2 assay polymerase chain reaction (PCR) with homogenous real-time fluorescent detection.

All organs were examined at autopsy. However, the examination of the heart and lungs forms the subject of discussion. The right lung and the left lung weighed 660g (RR; 360-570g) and 450g (RR; 325-480 g) respectively and were consolidated and congested. There was no macroscopic pulmonary embolism. The heart weighed 350g (RR; 270-360g) with a left ventricular thickness of 12mm.The coronaries were patent. There were no valvular lesions, and there was no gross myocardial injury, past or present.

2.1.1 Heart

The pathological findings were those seen in the illness stage of acute Covid-19. There was thrombosis of the capillary network of the myocardium. Fibrin thrombi were formed within the wall of the capillaries in the abluminal space between endothelial cells and the basement membrane, and not within the lumen (Figure 1).

Figure 1. H&E 10x20 shows a capillary with A (arrows) showing subendothelial/abluminal space fibrin thrombi and B (arrows) rupture/destruction of the capillary wall amongst myocardial fibres (C) – illness phase of acute Covid-19.



Fibrin thrombi were also formed within the walls in subendothelial layer/abluminal spaces of arterioles, veins, and venules (Figure 2 and 3). Fibrin thrombi were also present in the subendothelial/vasa interna location which extended into the media of the epicardial coronary artery namely the left anterior descending branch coronary artery (Figure 4). Injury or destruction of thrombosed microvascular network was evident. Fibrin was present encircling myocardial fibres in a diffuse but focal pattern (Figure 5 and 6). Fibrin encased myocardial fibres were seen in varying stages of atrophy/degeneration. Hemosiderin granules were present amongst degenerating myocardial fibres. There was no cellular inflammatory reaction associated with stromal fibrin. These observations were noted in the myocardium of patient 1.

Figure 2. H&E 10x20 shows a venule with subendothelial / abluminal space deposit (A) and (B) fibrin encasement of myocardial fibres of left ventricle- illness phase of acute Covid-19.

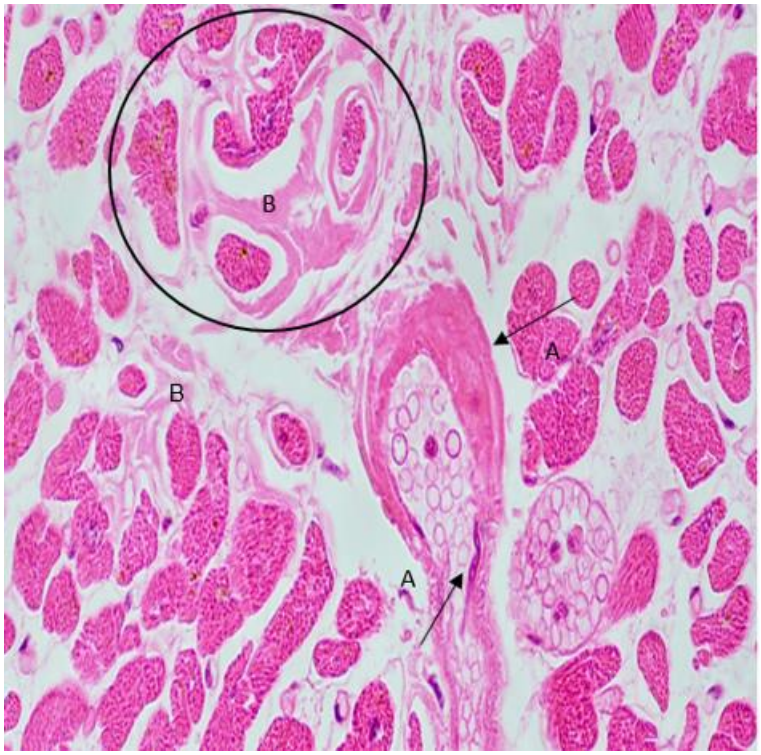


Figure 3. H&E 10x40 shows an arteriole with (A) thrombi formation within the wall but not within the lumen – illness phase of acute Covid-19.

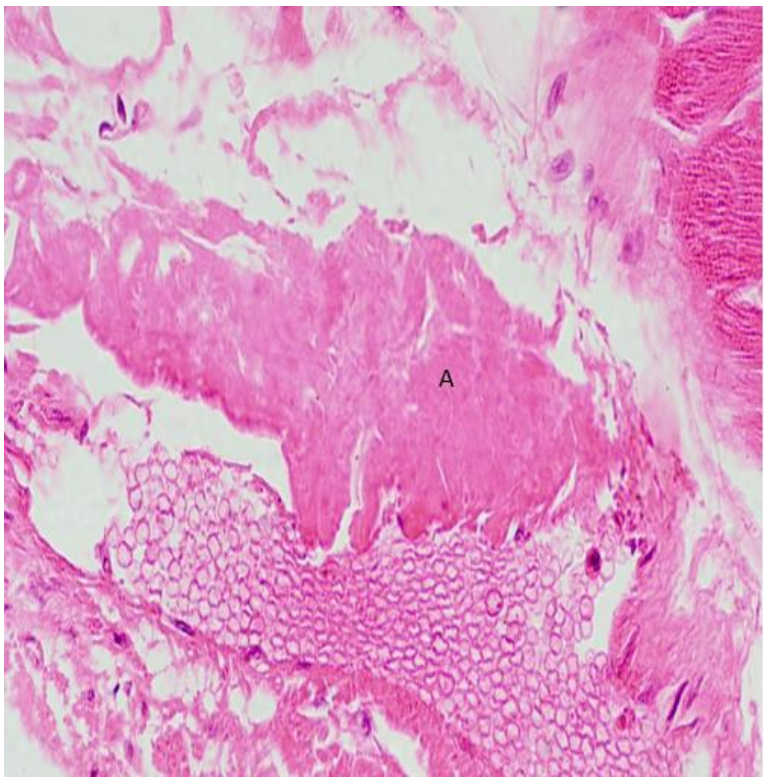


Figure 4. H&E 10x40 shows the left anterior descending branch of the coronary artery with (A) subendothelial deposit (which is the location of the vasa internae) rupturing into the wall (B) but not within the lumen. The area (C) might represent the genesis of the arterial dissection – illness phase of acute Covid-19.

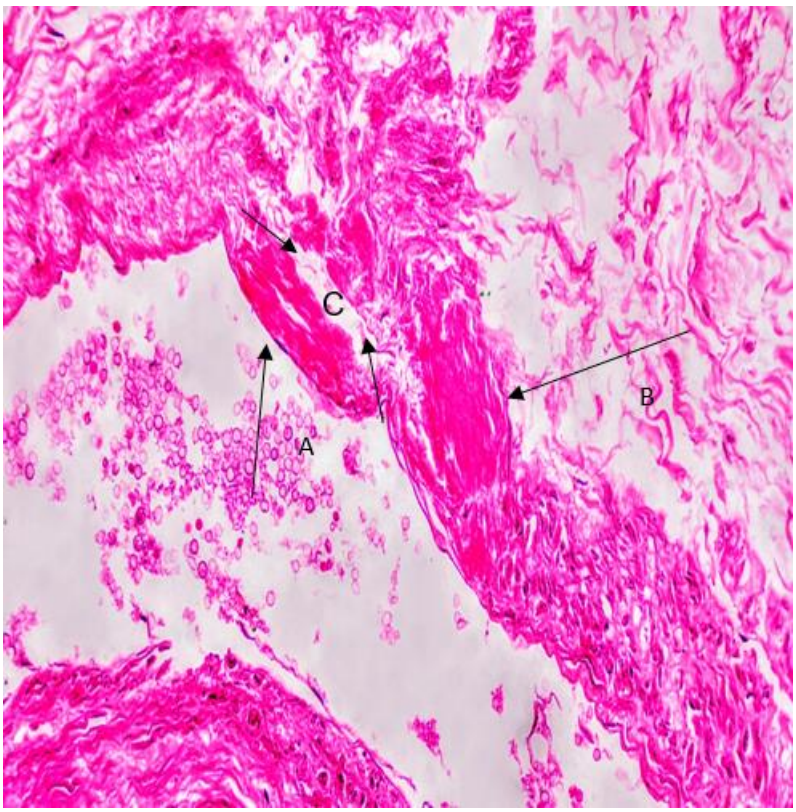


Figure 5. H&E 10x20 shows fibrin (A) deposited among the myocardial fibres without an inflammatory cellular infiltrate during the illness stage of acute Covid-19.

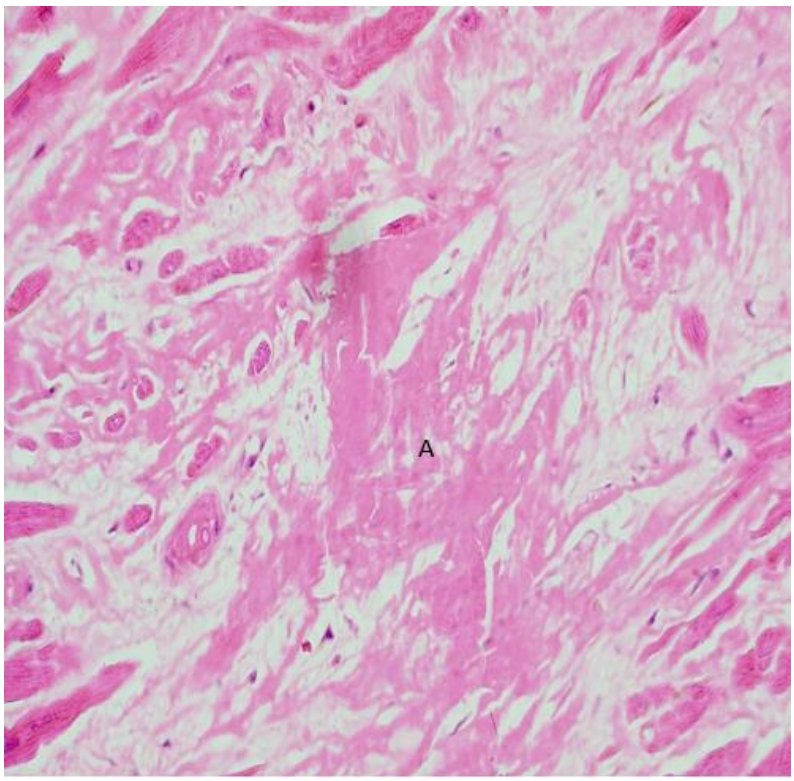
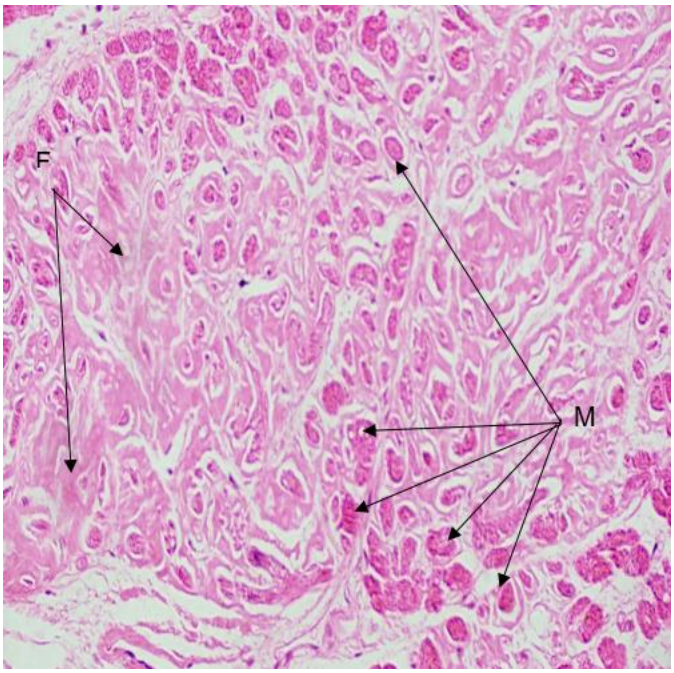


Figure 6. H&E 10x10 shows fibrin encasement (F) and destruction of myocardial fibres (M) of the right ventricle, without an inflammatory cellular infiltrate during the illness phase of acute Covid-19. This progresses to myocardial fibrosis during the stage of decline in acute Covid-19.



2.1.2 Lung

In patient 1 in the illness phase of acute Covid-19, fibrin thrombi were seen in the vascular network of the lung in the abluminal space of capillaries (see Figure 7), venules, arterioles and within large pulmonary vessels. Fibrin thrombi were also present in the adventitia of large pulmonary vessels (the vasa vasorum externa) (see Figure 8), and the abluminal spaces (the vasa vasorum internae). Fibrin thrombi were also seen within the abluminal spaces of the alveoli. These microscopic findings occurred simultaneously with those seen in the vascular network of the myocardium.

Figure 7. H&E 10x20 shows subendothelial/ abluminal space fibrin deposit (F) in alveolar capillary. Enlargement of these fibrin deposits gradually occludes the capillary lumen.

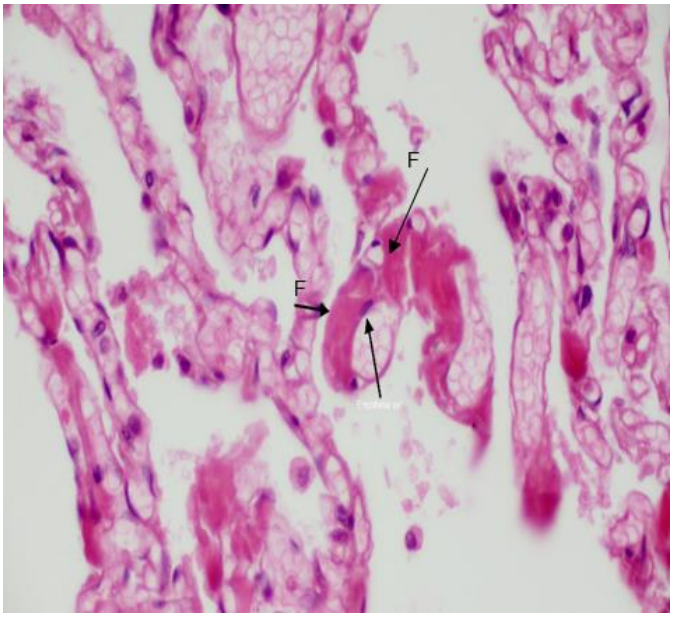
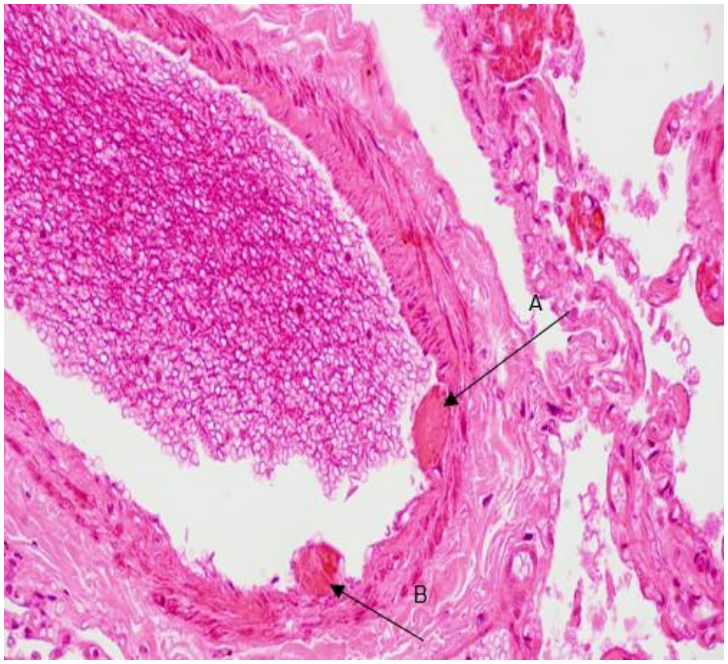


Figure 8. H&E 10 x 40 shows two subendothelial thrombi, (A) and (B) the regions of vasa internae in the pulmonary artery in the illness phase of acute Covid-19. These thrombi ultimately embolise within the pulmonary artery.



2.2 Patient 2

This was a 56-year-old female who had a cough, fever and shortness of breath and died at her residence, without medical intervention, some 15 days after her illness began. She suffered from no chronic disease. At autopsy her nasopharyngeal swab tested positive for SARS-COV-2 using Abbott Real-time SARS-CoV-2 assay polymerase chain reaction (PCR) with homogenous real-time fluorescent detection.

All her organs were examined by one pathologist at autopsy taking the necessary precaution. However, the examination of her heart and lung forms the subject of this discussion. The heart weighed 300g (RR; 270-360g). The coronary arteries were patented. There were no plaques. The left ventricular thickness measured 10mm. There was no macroscopic myocardial injury past or present, save for pallor. The right and left lung weighed 400g (RR; 360-570g) and 550 g (RR; 325-480 g) respectively and were congested. There was no pulmonary embolism.

Histological examination of autopsy specimens from all organs was done after staining with Hematoxylin and Eosin stains. There were two distinct pathological findings seen in the illness phase of acute Covid-19 and those seen in the decline phase of Covid-19.

2.2.1 Heart

In patient 2 the findings were suggestive of those seen in a convalescent stage or period of decline in acute Covid-19. The findings in the heart were those of diffuse focal myocardial fibrosis without a cellular inflammatory exudate. Thrombosis of the microcirculation was sparse (see Figures 9 and 10).

2.2.2 Lung

The findings in the lung were fibrosis of alveoli and thickening of vessel walls. Thrombosis was sparse and was observed in large pulmonary vessels only. These observations most likely corresponded to the period of decline in the acute phase of Covid-19 (see Figure 11).

Figure 9. H&E 10x10 shows focal fibrosis (F) of the myocardium during the stage of decline in acute Covid-19.

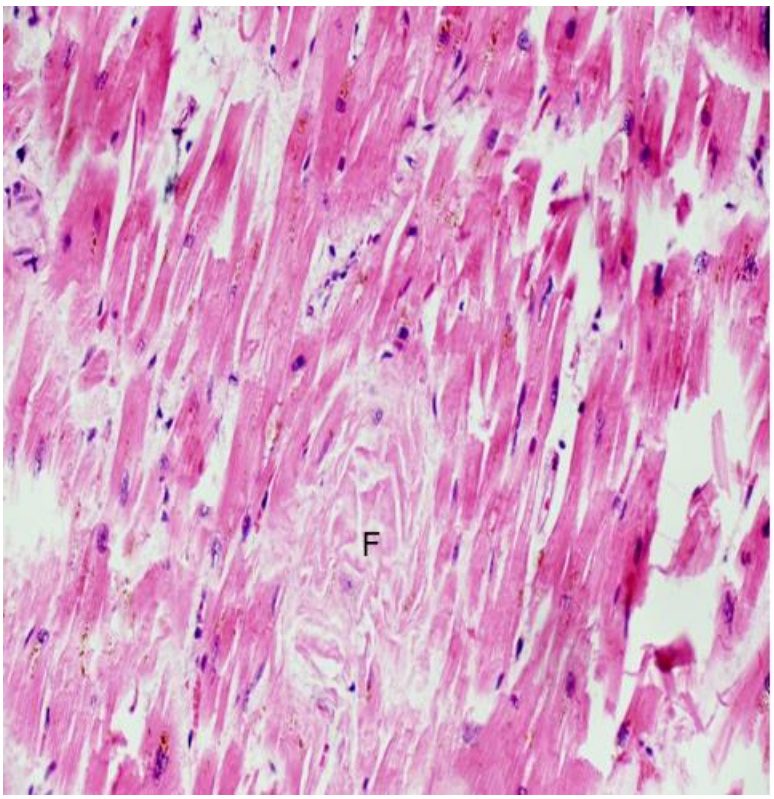


Figure 10. H&E 10x20 shows focal fibrosis (F) of the myocardium.

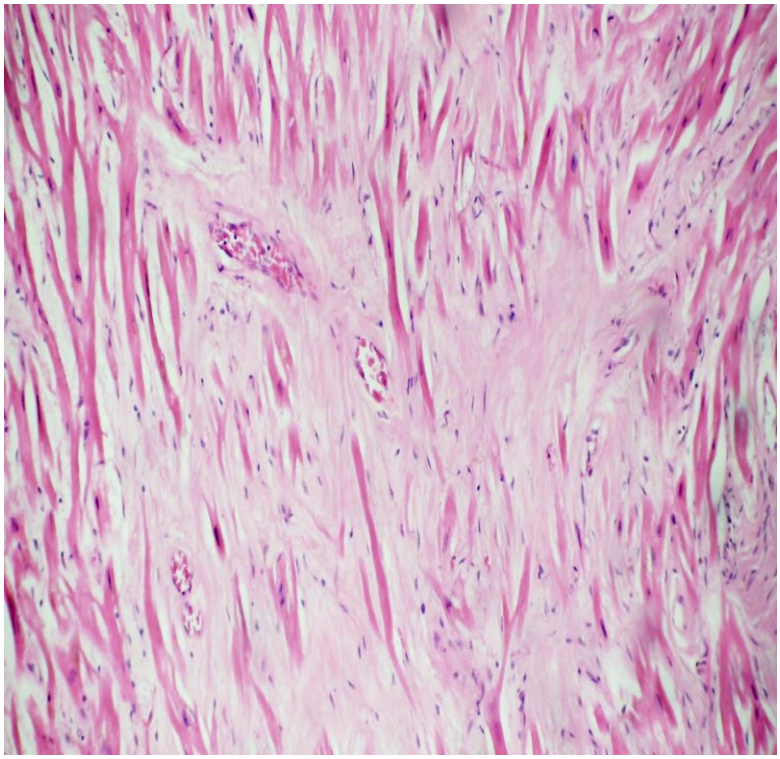
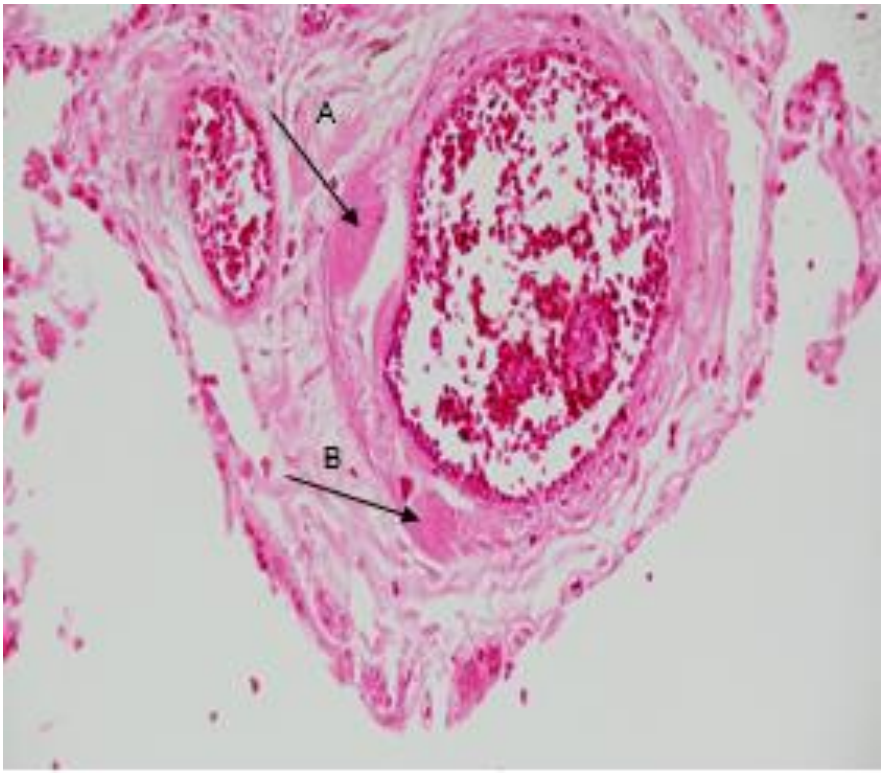


Figure 11. H&E 10x20 Fibrin thrombi within the vessel wall, vasa externa (A) and (B), in a pulmonary arteriole in stage of decline.



3. Discussion

3.1 Cardiac Pathology in Covid-19

A comprehensive understanding of the pathophysiology of the Heart in Covid-19 and the relevance of Covid-19 as it impacts comorbid states such as Diabetes mellitus and Essential Hypertension has not been fully elucidated. Instead, the English literature has been inundated with fragmented reports on the pathology of the heart in Covid-19 [5]. Our observational study serves to provide insights into the better understanding of the pathophysiology of the heart in Covid-19 which would contribute towards therapy.

Portions of the pathological impact of Covid-19 on the heart have been documented in both live patients and autopsies [6-8]. The literature highlights microvascular thrombosis and, to some extent, epicardial thrombosis [8-10] in Covid-19 yet the specific sites and pathophysiology of these microthrombi were not extensively detailed by any single author. Guagliumi and Sonzogni [10] reported microthrombi and ST-segment elevation myocardial infarction in a 43-year-old female patient with elevated troponin who had no obstructive coronary artery disease by angiogram. This patient succumbed to Covid-19, and her autopsy revealed intramyocardial small vessel thrombi with necrosis in both ventricles, contributing to myocardial injury in the absence of coronary epicardial thrombosis. Fibrin and platelet deposits were observed within myocardial tissue, like findings in our study during the illness stage of acute Covid-19. However, we observed additional epicardial vessel thrombosis and abluminal space fibrin deposits within vessels, which were not reported in their study [10].

In an autopsy study by Bois and Boire [8], nonocclusive fibrin microthrombi were identified in the myocardium. These nonocclusive fibrin deposits went unnoticed as localized in the abluminal spaces of micro vessels, as seen in our findings [11, 12] neither did the authors report fibrin deposits encircling myocardial fibres [8]. Pellegrini and Kawakami [13] found microthrombi in 9 of 14 hearts in patients dying of Covid-19, primarily

within myocardial capillaries, arterioles, and small arteries, with compositions rich in fibrin and terminal complement C5B-9. However, neither the specific location of these deposits within the vessel walls was mentioned, nor were fibrin deposits among myocardial fibres.

3.2 Patterns of Myocardial Pathology in Covid-19

In patients dying of severe Covid-19 without medical intervention, we observed two main patterns of myocardial pathology at autopsy: first, illness Stage of acute Covid -19, characterized by frequent fibrin thrombi in the coronary microvascular network, with fibrin encasement of myocardial fibres of both ventricles (see Figure 6). This fibrin encasement likely leads to myocardial fibre necrosis and accounts for the clinical cardiac manifestations in both acute and long Covid-19 [6, 14-16]. Fibrin thrombi were observed in the abluminal space, particularly where pericytes reside, rather than within the vascular lumen. Progressive enlargement of these subendothelial fibrin deposits can occlude vessels, like the pathology observed in alveolar capillaries [12] (see Figure 7). Secondly, during the decline or convalescent phase of acute COVID-19, myocardial pathology transitions to progressive myocardial injury over time. This leads to diffuse focal fibrosis affecting both cardiac ventricles, accompanied by reduced vascular thrombosis (see Figure 10). This fibrosis likely reflects earlier myocardial damage caused by fibrin encasement during the acute phase of the illness.

3.3 Vasa Vasorum Thrombosis in Covid-19

The vasa vasorum, small vessels around larger vessels, are essential for nourishing vessel walls thicker than 1 mm. The vasa play a critical role in the pathology of Covid-19-related mural thrombosis. This phenomenon is noted particularly in the epicardial coronary arteries. The vasa vasorum externa originate in the adventitia and supply the vessel wall, while the vasa vasorum interna arise from the vessel lumen and extend into the wall. In our study, we observed vasa vasorum thrombosis in the epicardial left anterior descending coronary artery during the illness stage of acute Covid-19, as well as in the pulmonary vasculature (see Figures 4 and 8) [17-21].

This epicardial thrombosis in the left coronary artery extends from the subendothelial/abluminal space to involve the media. This phenomenon might be the catalyst for spontaneous dissection of epicardial cardiac vessels seen in Covid-19 [22] (see Figure 4). Faa and Gerosa [23], reported aortic vasa vasorum thrombosis in Covid-19, emphasizing the significance of vasa vasorum thrombosis in disease pathophysiology. This pathology [24] aligns with our findings in coronary arteries and pulmonary vessels vasa vasorum thrombosis [19, 20]. The association of Covid-19 and acute aortic dissection has been reported in the literature [24, 25]. We postulate that the mechanism of the aortic dissection might be related to vasa internae thrombosis as evidenced by our observations. Gorecka and Thirunavukarasu [26] identified thrombi in the left anterior coronary artery lumen of a Covid-19 patient, likely originating from subendothelial/vasa vasorum internae thrombi that subsequently embolized, a process implicated in both large pulmonary arteries and epicardial vessels (See Figure 8) [20].

3.4 Role of Cardiac Pericytes in Microvascular Thrombosis

Cardiac Pericytes, residing in the abluminal space of the coronary vasculature, play a central role in fibrin thrombus formation [27]. These cells, with dendritic extensions that support endothelial cells through gap junctions and adhesion plaques, contribute to structural integrity and facilitate small molecule exchange across the capillary wall [28]. Under inflammatory conditions like cytokine storms, as seen in Covid-19, these gaps widen, allowing plasma fibrinogen, platelets, and other blood cells to enter abluminal spaces, promoting thrombus formation [29-32].

Pericytes also express ACE-2 receptors, the binding site for SARS-CoV-2, potentially making them targets for infection or spike protein interaction, contributing to coagulopathy. Juchem and Weiss [33] identified a subendothelial pericyte network, enriched with tissue factor in healthy vessels, particularly in venous intima, which promotes coagulation [33]. Andreeva and Pugach [34] documented pericyte-like cells in large, medium, and small vessels, including in the vasa vasorum [34]. Consistent with these findings, we found fibrin thrombi deposits in those pericyte-rich areas mentioned above [11, 12]. Cardiac pericytes, with their high ACE-2 receptor concentration, are susceptible to SARS-CoV-2 infection, potentially triggering a local procoagulant response and micro thrombosis [28, 35]. Alternative hypotheses suggest pericyte dysfunction in response to viral spike protein interactions with CD147 receptors, resulting in microvascular thrombosis and cardiac injury [36, 37].

3.5 Mechanisms of Myocardial Damage in Covid-19

Thrombosis of the coronary microcirculation in Covid-19 impedes nutrient and oxygen exchange, leading to hypoxic injury and myocardial fibre necrosis. Mechanical heart action during systole and diastole may lead to rupture of thrombosed micro vessels, allowing fibrin infiltration among myocardial fibres. Additionally, fibrin encasement of myocardial fibres from thrombosed vessels exacerbates fibre damage, resulting in progressive damage and fibrosis, causing clinical manifestations as seen in ischemic heart disease. This is most likely the pathophysiology of ischaemic heart disease experienced in long covid, which occurs in the absence of epicardial vessels blockage. The fragility of capillaries in elderly patients with diabetes mellitus or hypertension exacerbates vessel rupture, potentially leading to more severe Covid-19 [38]. The pathology in myocardial tissue mirrors changes observed in the pulmonary vasculature, underscoring the systemic impact of microvascular thrombosis in Covid-19.

4. Conclusion

The findings emphasize that Covid-19's myocardial pathology predominantly arises from fibrin thrombi within the coronary microvascular network, especially in the abluminal spaces. This pathological process leads to myocardial fibre injury, necrosis, and ischemic changes, contributing to both the acute symptoms and long-term sequelae (Long Covid). The evidence points to a mechanism where mechanical stress from heartbeats might exacerbate vessel rupture and fibrin encasement, progressively damaging myocardial fibres and resulting in ischemic heart disease symptoms. Epicardial vessel mural thrombosis caused by thrombosis of vasa internae, might result in thromboembolism in these vessels and may be the genesis of spontaneous coronary artery dissection seen in Covid-19. The role of pericytes is central in thrombus formation, especially due to their location and high ACE-2 receptor expression, making them a significant factor in Covid-19 cardiac pathology.

Although only two cases were presented in this study, the findings highlight the anatomical pathology of the myocardium in severe Covid-19 and underline a pathological mechanism common to both cardiac and pulmonary circulation [11, 12, 20] emphasizing the systemic impact of Covid-19 on the microvascular network.

Funding: Not applicable.

Research Ethics Committee Approval: We declare that the patient approved the study by signing the informed consent form, and that the study followed the ethical guidelines established by the Declaration of Helsinki.

Acknowledgments: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Lowenstein CJ, Solomon SD. Severe COVID-19 Is a Microvascular Disease. Circulation. 2020 Oct 27;142(17):1609-1611. doi: 10.1161/CIRCULATIONAHA.120.050354. Epub 2020 Sep 2. PMID: 32877231; PMCID: PMC7580651.
2. Karakasis P, Nasoufidou A, Sagris M, Fragakis N, Tsioufis K. Vascular Alterations Following COVID-19 Infection: A Comprehensive Literature Review. Life (Basel). 2024 Apr 24;14(5):545. doi: 10.3390/life14050545. PMID: 38792566; PMCID: PMC11122535.
3. Çalışkan M, Baycan ÖF, Çelik FB, Güvenç TS, Atıcı A, Çağ Y, Konal O, İrgi T, Bilgili ÜZ, Ağırbaşlı MA. Coronary microvascular dysfunction is common in patients hospitalized with COVID-19 infection. Microcirculation [Internet]. 2022 Apr 19;29(4–5). Available from: https://doi.org/10.1111/micc.12757.
4. Wadowski PP, Panzer B, Józkowicz A, Kopp CW, Gremmel T, Panzer S, Koppensteiner R. Microvascular thrombosis as a critical factor in severe COVID-19. International Journal of Molecular Sciences [Internet]. 2023 Jan 27;24(3):2492. Available from: https://doi.org/10.3390/ijms24032492.
5. Azevedo RB, Botelho BG, Hollanda JVG, Ferreira LVL, Junqueira de Andrade LZ, Oei SSML, Mello TS, Muxfeldt ES. Covid-19 and the cardiovascular system: a comprehensive review. J Hum Hypertens. 2021 Jan;35(1):4-11. doi: 10.1038/s41371-020-0387-4. Epub 2020 Jul 27. PMID: 32719447; PMCID: PMC7384729.
6. Kole C, Stefanou E, Karvelas N, Schizas D, Toutouzas KP. Acute and Post-Acute COVID-19 Cardiovascular Complications: A Comprehensive review. Cardiovascular Drugs and Therapy [Internet]. 2023 May 20; Available from: https://doi.org/10.1007/s10557-023-07465-w.
7. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, Ibrahim H, Friedman GH, Thompson C, Alviar CL, Chadow HL, Fishman GI, Reynolds HR, Keller N, Hochman JS. ST-Segment Elevation in Patients with Covid-19 — A Case Series. New England Journal of Medicine [Internet]. 2020 Apr 17;382(25):2478–2480. Available from: https://doi.org/10.1056/nejmc2009020.
8. Bois MC, Boire NA, Layman AJ, Aubry MC, Alexander MP, Roden AC, Hagen CE, Quinton RA, Larsen C, Erben Y, Majumdar R, Jenkins SM, Kipp BR, Lin PT, Maleszewski JJ. COVID-19–Associated nonocclusive fibrin microthrombi in the heart. Circulation [Internet]. 2020 Nov 16;143(3):230–243. Available from: https://doi.org/10.1161/circulationaha.120.050754.
9. Yin J, Wang S, Liu Y, Chen J, Li D, Xu T. Coronary microvascular dysfunction pathophysiology in COVID-19. Microcirculation [Internet]. 2021 May 20;28(7). Available from: https://doi.org/10.1111/micc.12718.
10. Guagliumi G, Sonzogni A, Pescetelli I, Pellegrini D, Finn AV. Microthrombi and ST-Segment–Elevation myocardial infarction in COVID-19. Circulation [Internet]. 2020 Jul 17;142(8):804–809. Available from: https://doi.org/10.1161/circulationaha.120.049294.
11. Daisley H, Rampersad A, Daisley M, Ramdin A, Acco O, Narinesingh F, Humphrey O. COVID-19: a closer look at the pathology in two autopsied cases. Is the pericyte at the center of the pathological process in COVID-19? Autopsy and Case Reports [Internet]. Hospital Universitário da Universidade de São Paulo; 2021 May 6;11. Available from: http://www.scielo.br/pdf/acrep/v11/2236-1960-acrep-11-e2021262.pdf.
12. Daisley H, Acco O, Daisley M, George D, Paul L, Rampersad A, Daisley J. COVID-19 shed light on Virchow's law of thrombosis. Autopsy and Case Reports [Internet]. 2024 Jan 1;14:e2024512. Available from: https://doi.org/10.4322/acr.2024.512.
13. Pellegrini D, Kawakami R, Guagliumi G, Sakamoto A, Kawai K, Gianatti A, Nasr A, Kutys R, Guo L, Cornelissen A, Faggi L, Mori M, Sato Y, Pescetelli I, Brivio M, Romero M, Virmani R, Finn AV. Microthrombi as a major cause of cardiac injury in COVID-19. Circulation [Internet]. 2021 Jan 22;143(10):1031–1042. Available from: https://doi.org/10.1161/circulationaha.120.051828.
14. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nature Medicine [Internet]. 2022 Feb 7;28(3):583–590. Available from: https://doi.org/10.1038/s41591-022-01689-3.
15. Cremer S, Jakob C, Berkowitsch A, Borgmann S, Pilgram L, Tometten L, Classen A, Wille K, Weidlich S, Gruener B, Dimmeler S, Massberg S, Rieg S, Zeiher AM. Elevated markers of thrombo-inflammatory activation predict outcome in patients with cardiovascular comorbidities and COVID-19 disease: insights from the LEOSS registry. Clinical Research in Cardiology [Internet]. 2020 Nov 19;110(7):1029–1040. Available from: https://doi.org/10.1007/s00392-020-01769-9.
16. Gyöngyösi M, Alcaide P, Asselbergs FW, Brundel BJJM, Camici GG, Da Costa Martins P, Ferdinandy P, Fontana M, Girao H, Gnecchi M, Gollmann-Tepeköylü C, Kleinbongard P, Krieg T, Madonna R, Paillard M, Pantazis A, Perrino C, Pesce M, Schiattarella GG, Sluijter JPG, Steffens S, Tschöpe C, Van Linthout S, Davidson SM. Long COVID and the cardiovascular system — elucidating causes and cellular mechanisms in order to develop targeted diagnostic and therapeutic strategies: a joint Scientific Statement of the ESC Working Groups on Cellular Biology of the Heart and Myocardial and Pericardial Diseases. Cardiovascular Research [Internet]. 2022 Jul 25;119(2):336–356. Available from: https://doi.org/10.1093/cvr/cvac115.
17. Gössl M, Rosol M, Malyar NM, Fitzpatrick LA, Beighley PE, Zamir M, Ritman EL. Functional anatomy and hemodynamic characteristics of vasa vasorum in the walls of porcine coronary arteries. The Anatomical Record Part a Discoveries in Molecular Cellular and Evolutionary Biology [Internet]. 2003 Apr 23;272A(2):526–537. Available from: https://doi.org/10.1002/ar.a.10060).
18. Williams JK, Heistad DD. Structure and function of vasa vasorum. Trends in Cardiovascular Medicine [Internet]. 1996 Feb 1;6(2):53–57. Available from: https://doi.org/10.1016/1050-1738(96)00008-4.
19. Daisley H Junior, Rampersad A, Daisley M, Ramdin A, Acco O, Narinesingh F, Humphrey O, James E. The vasa vasorum of the large pulmonary vessels are involved in COVID-19. Autopsy and Case Reports [Internet]. 2021 Jan 1;11:e2021304. Available from: https://doi.org/10.4322/acr.2021.304.

20. Daisley H, Acco O, Daisley M, George D, Paul L, James E, Rampersad A, Narinesingh F, Humphrey O, Daisley J, Nathan M. Thrombosis of the vasa vasorum of the large and medium size pulmonary artery and vein leads to pulmonary thromboembolism in COVID-19. Autopsy and Case Reports [Internet]. 2024 Jan 1;14:e2024491. Available from: https://doi.org/10.4322/acr.2024.491.
21. Huang W, Richards TD, Kaczorowski DJ, Noda K, Bartholow T, Sanchez PG, Phillippi JA. Pulmonary artery vasa vasorum damage in severe COVID-19 induced pulmonary fibrosis. Annals of Thoracic Surgery Short Reports [Internet]. 2024 Jan 1; Available from: https://doi.org/10.1016/j.atssr.2023.12.019.
22. Tsigkas G, Bozika M, Nastouli KM, Apostolos A, Routoula M, Georga AM, Latta A, Papageorgiou A, Papafaklis MI, Leventopoulos G, Karamasis GV, Davlouros P. Spontaneous Coronary Artery Dissection and COVID-19: A Review of the Literature. Life (Basel). 2024 Feb 28;14(3):315. doi: 10.3390/life14030315. PMID: 38541641; PMCID: PMC10970992.
23. Faa G, Gerosa C, Fanni D, Barcellona D, Cerrone G, Orrù G, Scano A, Marongiu F, Suri JS, Demontis R, Nioi M, D'Aloja E, La Nasa G, Saba L. Aortic vulnerability to COVID-19: is the microvasculature of vasa vasorum a key factor? A case report and a review of the literature. DOAJ (DOAJ: Directory of Open Access Journals) [Internet]. 2021 Oct 1;25(20):6439–6442. Available from: https://doaj.org/article/36b047c3471d421eacc0ef4fe94365ef.
24. Irilouzadian R, Salehi Omran H, Alirezaei T. Fatal association of COVID-19 and acute type A aortic dissection. Clin Case Rep. 2022 Mar 22;10(3):e05617. doi: 10.1002/ccr3.5617. PMID: 35356160; PMCID: PMC8939039.
25. Engin M, Aydın U, Eskici H, Ata Y, Türk T. Type 1 Acute Aortic Dissection in the Early Period After COVID-19 Infection. Cureus. 2021 Mar 7;13(3):e13751. doi: 10.7759/cureus.13751. PMID: 33842128; PMCID: PMC8023408.
26. Gorecka M, Thirunavukarasu S, Levelt E, Greenwood JP. Multiple etiologies to myocardial injury in COVID-19. JACC Case Reports [Internet]. 2021 Jun 1;3(6):971–972. Available from: https://doi.org/10.1016/j.jaccas.2021.05.003.
27. Das M, Chung MK. Cardiac pericytes. JACC Basic to Translational Science [Internet]. 2023 Feb 1;8(2):121–123. Available from: https://doi.org/10.1016/j.jacbts.2023.01.010.
28. Zhang ZS, Zhou HN, He SS, Xue MY, Li T, Liu LM. Research advances in pericyte function and their roles in diseases. Chinese Journal of Traumatology [Internet]. 2020 Mar 6;23(2):89–95. Available from: https://doi.org/10.1016/j.cjtee.2020.02.006
29. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. New England Journal of Medicine [Internet]. 2020 May 21;383(2):120–128. Available from: https://doi.org/10.1056/nejmoa2015432.
30. Cardot-Leccia N, Hubiche T, Dellamonica J, Burel-Vandenbos F, Passeron T. Pericyte alteration sheds light on micro-vasculopathy in COVID-19 infection. Intensive Care Medicine [Internet]. 2020 Jun 12;46(9):1777–1778. Available from: https://doi.org/10.1007/s00134-020-06147-7.
31. Cadamuro M, Lasagni A, Radu CM, Calistri A, Pilan M, Valle C, Bonaffini PA, Vitiello A, Toffanin S, Venturin C, Friòn-Herrera Y, Sironi S, Alessio MG, Previtali G, Seghezzi M, Gianatti A, Strazzabosco M, Strain AJ, Campello E, Spiezia L, Palù G, Frigo AC, Tosoni A, Nebuloni M, Parolin C, Sonzogni A, Simioni P, Fabris L. Procoagulant phenotype of virus-infected pericytes is associated with portal thrombosis and intrapulmonary vascular dilations in fatal COVID-19. Journal of Hepatology [Internet]. 2024 Jun 1; Available from: https://doi.org/10.1016/j.jhep.2024.06.014
32. Unipd Research. Microthrombosis, Severe Liver Disease, and Fatal COVID-19. 5th July 2024. Available from: https://www.unipd.it/news/unipd-research-microthrombosis-severe-liver-disease-and-fatal-covid-19unipd-research.
33. Juchem G, Weiss DR, Gansera B, Kemkes BM, Mueller-Hoecker J, Nees S. Pericytes in the macrovascular intima: possible physiological and pathogenetic impact. AJP Heart and Circulatory Physiology [Internet]. 2009 Dec 19;298(3):H754–H770. Available from: https://doi.org/10.1152/ajpheart.00343.2009.
34. Andreeva ER, Pugach IM, Gordon D, Orekhov AN. Continuous subendothelial network formed by pericyte-like cells in human vascular bed. Tissue and Cell [Internet]. 1998 Feb 1;30(1):127–135. Available from: https://doi.org/10.1016/s0040-8166(98)80014-1.
35. Brumback BD, Dmytrenko O, Robinson AN, Bailey AL, Ma P, Liu J, Hicks SC, Ng S, Li G, Zhang DM, Lipovsky CE, Lin CY, Diamond MS, Lavine KJ, Rentschler SL. Human cardiac pericytes are susceptible to SARS-COV-2 infection. JACC Basic to Translational Science [Internet]. 2022 Sep 14;8(2):109–120. Available from: https://doi.org/10.1016/j.jacbts.2022.09.001.
36. Avolio E, Carrabba M, Milligan R, Williamson MK, Beltrami AP, Gupta K, Elvers KT, Gamez M, Foster RR, Gillespie K, Hamilton F, Arnold D, Berger I, Davidson AD, Hill D, Caputo M, Madeddu P. The SARS-CoV-2 Spike protein disrupts human cardiac pericytes function through CD147 receptor-mediated signalling: a potential non-infective mechanism of COVID-19 microvascular disease. Clinical Science [Internet]. 2021 Nov 22;135(24):2667–2689. Available from: https://doi.org/10.1042/cs20210735.
37. Tsai EJ, Čiháková D, Tucker NR. Cell-Specific mechanisms in the heart of COVID-19 patients. Circulation Research [Internet]. 2023 May 11;132(10):1290–1301. Available from: https://doi.org/10.1161/circresaha.123.321876.
38. Beaser SB, Rudy A, Seligman A. CAPILLARY FRAGILITY IN RELATION TO DIABETES MELLITUS, HYPERTENSION AND AGE. Archives of Internal Medicine [Internet]. 1944 Jan 1;73(1):18. Available from: https://doi.org/10.1001/archinte.1944.002101300260.