Objective and method From January to May 2020, 113 patients were admitted in ICU for severe COVID-19. All these patients underwent continuous monitoring of their cardiac rhythm. Ten patients (9%) presented a bradycardia. A 24-hour Holter-ECG was subsequently performed for 7 patients.
Results Patients had a median age of 63 years. Most of them were men and had severe acute respiratory distress syndrome. All episodes were due to sinus bradycardia with a median heart rate of 36 bpm. Bradycardia was sudden for four patients and required brief resuscitation maneuvers for one. Bradycardia was persistent for the six other patients and required transient continuous isoprenaline infusion for three. Patients had normal baseline ECG and echocardiography. A comprehensive review of patient's files ruled out bradycardia due to drug-drug interactions, myocarditis, hyperkalemia, hypoxia or vagal physical stimulation. Two patients had beta-blockers interrupted several days before bradycardia and one patient received Hydroxychloroquine discontinued 21 days before bradycardia. On the Holter-ECG, 3 recordings evoked vagal hyperactivity (low mean heart rate and elevated pNN50/RMSSD, Fig. 1, patient A), 3 others cardiac dysautonomia (SDNN < 100 ms, Fig. 1, patient B). Amongst these 10 patients, five returned home and five died from COVID-19 associated multiple-organ failure. None of them required temporary or permanent cardiac pacing (Fig. 1).
Conclusion We hypothesized that bradycardia may be due to an autonomic nervous system injury. The parallel course of COVID-19 and bradycardia suggest that these patients do not have intrinsic sinus node disease and that pacemaker implantation should not be recommended.

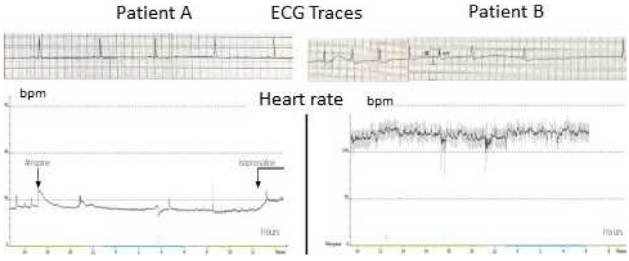

Fig. 1 Representative ECG and Holter-ECG traces.

Disclosure of interest The authors declare that they have no competing interest.

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Role of oxygen exposure on the differentiation of human induced pluripotent stem cells in 2D and 3D cardiac organoids

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Introduction Human induced pluripotent stem cells (hiPSC) have the ability to differentiate theoritically into any cell type. The development of organoid systems exhibiting the essential features of human organ such as liver and heart is of high interest. Optimizing the culture conditions to obtain the highest cardiac organoids efficacy is crucial. In fact, cardiac differentiation protocols have been established by essentially focusing on specific growth factors on hiPSC differentiation efficiency. However, the optimal environmental factors such as the optimal oxygen exposure to obtain cardiac myocytes in network are still unclear. The mesoderm germ layer differentiation is known to be enhanced by low oxygen exposure. Yet, the effect of low oxygen exposure on the molecular and functional maturity of the hiPSC-derived cardiomyocytes remains unexplored.
Aims We aimed here at comparing the molecular and functional consequences of low (5% O_2 or LOE) and high oxygen exposure (21% O_2 or HOE) on cardiac differentiation of hiPSCs in 2D monolayer and 3D organoids protocols.
Methods hiPSC-CMs were differentiated through both the 2D (monolayer) and 3D (embryoid body) protocols using several lines. Cardiac marker expression and cell morphology were assessed using qRT-PCR and immunofluorescence. The mitochondrial localization and metabolic properties were evaluated by high-resolution respirometry and mitochondrial staining. The intracellular Ca^{2+} handling and contractile properties were also monitored using confocal fluorescent microscopy and atomic force microscopy.
Results Our results indicated that the 2D cardiac monolayer can only be differentiated in HOE. The 3D cardiac organoids containing hiPSC-CMs in LOE exhibited higher cardiac markers expression such as troponin T (TnTc), RyR2, Serca2a, alpha and beta heavy myosin chains. Moreover, we found enhanced contractile force, hypertrophy and steadier SR Ca^{2+} release reflected by a more regular spontaneous Ca^{2+} transients associated with a higher maximal amplitude and lower spontaneous Ca^{2+} events revealing a better SR Ca^{2+} handling in LOE. Similar beat rate, preserved distribution of mitochondria and similar oxygen consumption by the mitochondrial respiratory chain complexes were also observed.
Conclusions Our results brought evidences that LOE is moderately beneficial for the 3D cardiac organoids with hPSC-CMs exhibiting further maturity. In contrast, the 2D cardiac monolayers strictly require HOE.
Disclosure of interest The authors declare that they have no competing interest.

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CRISPR/Cas9-mediated generation of cardiomyocytes derived from human induced pluripotent stem cells to model SCN5A deficiency

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Introduction The cardiac voltage-gated sodium channel α-subunit ($Na_v1.5$), encoded by *SCN5A*, is a key determinant of cardiac excitability. Variants in *SCN5A* have been clearly identified as responsible for cardiac arrythmias, highlighting its critical role in cardiac physiology and heart diseases, such as Lev's disease or Brugada syndrome, two rare inherited cardiac arrhythmias associated with *SCN5A* loss-of-function mutations.