

We found evidence of ZIKV infection in amniotic epithelial cells and in fetal mesenchymal cells with affinity for perichondrium. Our observation indicates that ZIKV replicates in pluripotent (amniotic stem) cells involved in early-stage embryo development. The observation of prolonged viremia until day 21 in the patient is in concordance with the findings of Driggers et al.³ and provides further data for consideration in the ongoing development of testing algorithms in pregnant women. These algorithms are currently based on the assumption that ZIKV viremia can be detected only up to 7 days.

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1. Sarno M, Sacramento GA, Khouri R, et al. Zika virus infection and stillbirths: a case of hydrops fetalis, hydranencephaly and fetal demise. *PLoS Negl Trop Dis* 2016;10(2):e0004517.
2. Martines RB, Bhatnagar J, Keating MK, et al. Notes from the field: evidence of Zika virus infection in brain and placental tissues from two congenitally infected newborns and two fetal losses — Brazil, 2015. *MMWR Morb Mortal Wkly Rep* 2016;65:159-60.
3. Driggers RW, Ho C-Y, Korhonen EM, et al. Zika virus infection with prolonged maternal viremia and fetal brain abnormalities. *N Engl J Med* 2016;374:2142-51.

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Cheyne–Stokes Respiration, Chemoreflex, and Ticagrelor-Related Dyspnea

TO THE EDITOR: Dyspnea is a common side effect of the P2Y₁₂-receptor antagonist ticagrelor in patients who receive this drug after an acute coronary syndrome.^{1,2} Symptoms develop in a dose-dependent fashion and usually disappear on discontinuation of ticagrelor and with reductions in plasma levels of the drug.^{1,2} The mechanism of this side effect, which is unrelated to negative effects on cardiac and pulmonary function, is unknown.²

Here we describe the case of a patient (Patient 1) who was hospitalized for non–ST-segment elevation myocardial infarction. After the patient underwent complete revascularization for three-vessel coronary artery disease, double antiplatelet therapy with aspirin and ticagrelor was initiated. Within a few hours after the administration of ticagrelor, the patient began to report dyspnea, particularly at night and in the supine position, despite normal systolic and diastolic left ventricular function and normal pulmonary function. The results of the arterial blood gas analysis were normal, as were outcomes of pul-

monary function as assessed by spirometry, which was performed in conformity with the American Thoracic Society–European Respiratory Society standards and included measures of slow vital capacity, forced vital capacity, and forced expiratory volume in 1 second; static lung volumes; and the diffusing capacity of the lung for carbon monoxide.

One month later, during a visit for persisting dyspnea, the patient was observed to have an abnormal pattern of periodic breathing, with alternating apneas and hyperventilation. Thus, 24-hour cardiorespiratory monitoring was performed. As shown in Figure 1A (top), this monitoring revealed the presence of Cheyne–Stokes respiration (central apnea and hyperpnea), which occurred during both the night and the day. The rebreathing technique (i.e., a breathing circuit in which exhaled air is inhaled with or without absorption of carbon dioxide or oxygen) also showed increased chemosensitivity to hypercapnia (Fig. 1A, middle) and normal chemosensitivity to hypoxia.³

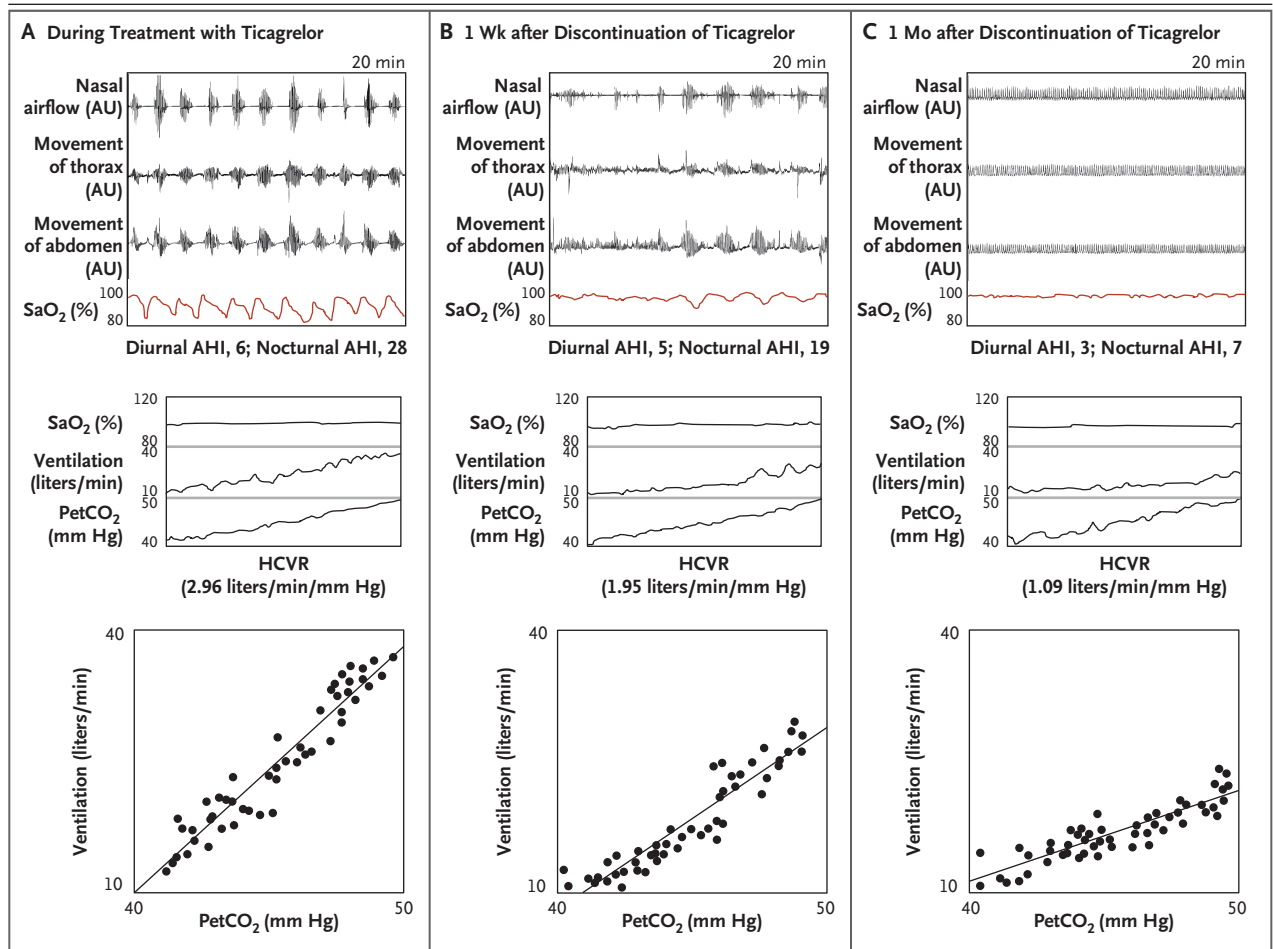


Figure 1. Results of 24-Hour Cardiorespiratory Monitoring and Chemosensitivity to Carbon Dioxide in Patient 1.

One month after the initiation of ticagrelor, Patient 1 had evidence of Cheyne–Stokes respiration (Panel A [top]). Diurnal and nocturnal scores on the apnea–hypopnea index (AHI, the number of occurrences of apnea or hypopnea per hour) are shown. The patient also had increased chemosensitivity to carbon dioxide while receiving ticagrelor (Panel A, middle and bottom). After discontinuation of the drug, the amelioration of symptoms occurred with progressive disappearance of Cheyne–Stokes respiration (Panels B, top, and C, top) and a reduction in chemoreflex sensitivity to hypercapnia (Panels B, middle and bottom, and C, middle and bottom). AU denotes arbitrary units, HCVR hypercapnic ventilatory response, PetCO₂ partial pressure of end-tidal carbon dioxide, and SaO₂ arterial oxygen saturation.

Immediately after the patient discontinued ticagrelor and switched to clopidogrel, the dyspnea attenuated and then disappeared. Serial evaluations of the patient's breathing pattern and chemosensitivity performed at 1 week and at 1 month after discontinuation of ticagrelor showed a progressive reduction, to normal values, of both the apnea–hypopnea index (AHI, the number of occurrences of apnea or hypopnea per hour) (Fig. 1B, top, and 1C, top) and chemosensitivity to hypercapnia (Fig. 1B, middle, and 1C, middle).

The same respiratory pattern was confirmed in three other patients who had normal cardio-

pulmonary function and who were screened for Cheyne–Stokes respiration 1 month after an acute coronary syndrome. In Patient 2, the diurnal AHI was 28 and the nocturnal AHI was 48. In Patient 3, the diurnal AHI was 41 and the nocturnal AHI 74, and in Patient 4, the diurnal AHI was 30 and the nocturnal AHI 58. In these three patients, ticagrelor was continued on the basis of a clinical decision, and in two patients, the follow-up confirmed the persistence of Cheyne–Stokes respiration. In Patient 2, the diurnal AHI after 1 week was 3 and the nocturnal AHI 35; in Patient 3, the diurnal AHI after 1 month was 13 and the nocturnal AHI 59.

The P2Y₁₂ receptor is expressed not only in platelets but also in other hematopoietic and nonhematopoietic cells, including microglia in the central nervous system,⁴ with potential purinergic stimulation of the chemoreflex system.⁵ This stimulation may elicit Cheyne–Stokes respiration. In a patient who receives ticagrelor and has persistent dyspnea, screening for Cheyne–Stokes respiration may be considered to address the patient's discomfort.

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1. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.
2. Storey RF, Bliden KP, Patil SB, et al. Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel, or placebo in the ONSET/OFFSET study. *J Am Coll Cardiol* 2010;56:185-93.
3. Giannoni A, Emdin M, Bramanti F, et al. Combined increased chemosensitivity to hypoxia and hypercapnia as a prognosticator in heart failure. *J Am Coll Cardiol* 2009;53:1975-80.
4. Gachet C. P2Y₁₂ receptors in platelets and other hematopoietic and non-hematopoietic cells. *Purinergic Signal* 2012;8:609-19.
5. Gourine AV, Kasymov V, Marina N, et al. Astrocytes control breathing through pH-dependent release of ATP. *Science* 2010;329:571-5.

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Contact Dr. Robert Wendel or Laura Wendel, 3939 J St., Suite 106, Sacramento, CA 95819; or call (916) 483-6299; or fax (916) 483-6297; or e-mail squawvalleyretina@comcast.net; or see <http://www.squawvalleyretina.com>.

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