

Original Research Article

Prevalence and Clinicoradiological Profiles of Respiratory Dysfunction in Patients with Medullary Infarction: Retrospective Case Study and Review of Literature

ABSTRACT

Background: Respiratory dysfunction occurs in stroke patients. Little is known about the prevalence, clinical features and lesion topography in patients with dyspnea due to medullary infarction (MI). We aimed to evaluate the frequency and the clinicoradiological profile in dyspnic MI patients.

Methods: We serially reviewed clinical records and magnetic resonance imaging (MRI) findings in 2144 inpatients (1211 men and 933 women) with acute ischemic stroke from 2007 to 2013. The clinicoradiological features were studied in MI patients with respiratory dysfunction. The prevalence of dyspnic MI was estimated among patients with cerebral infarction or MI. Patients with extensive infarction in the brainstem or the posterior circulation area, and cerebral hernia were excluded.

Results: Ninety-five patients (47 men and 48 women) were diagnosed as MI. Six patients (2 men and 4 women) developed respiratory dysfunction. The prevalence was 6.3% (4.3% in men and 8.3% in women) in MI patients, and 0.3% (0.2 % in men and 0.4% in women) in patients with cerebral infarction. Age was ranged from 38 to 78 years and the mean age (SD) was 70.0 (22.3) years. Abnormal respiration patterns included hyperventilation in 4 patients, dyspnea in one and apnea in one. Initial neurological examination revealed absent pharyngeal reflex and soft palatal palsy in all patients. Cough syncope, hiccup, dysphagia, circulatory failure, sensory deficits or dysuria was present simultaneously in several patients. MRI disclosed three types of lesion topography: 1) the bilateral medial and the right tegmental regions in the upper

26 and the middle medulla oblongata, 2) the right-predominant extensive regions in the
 27 lower medulla oblongata, and 3) the left lateral and tegmental regions in the lower
 28 medulla oblongata. Magnetic resonance angiography or cerebral angiography showed
 29 severe degree of atherosclerosis, dural arteriovenous fistula or dissection in the vertebral
 30 artery. The prognosis was fatal in 2 patients, poor in 2 patients, and recovered in each
 31 one patient with and without intervention.

32 **Conclusion:** The present study indicated that the prevalence of MI-induced respiratory
 33 dysfunction was 0.3% in patients with ischemic stroke and 6.3% in MI patients. The
 34 frequency of hypertension was highest on CVD risk factors. Absent pharyngeal reflex
 35 and soft palatal palsy were found on initial examination. The neurological profile
 36 suggested cough, hiccup, circulatory instability, bulbar palsy and dysuria. The urinary
 37 center and the circulatory center near the respiratory medullary center might be
 38 damaged. Radiological topography disclosed unilateral MI in 4 patients and bilateral MI
 39 in 2 patients. The pathognomonic lesions were found unilaterally or bilaterally in the
 40 medulla oblongata, including the tegmentum. Infarctive side and size were not
 41 correlated with the prognosis. The prognosis was fatal in 2 patients (33%). The
 42 atherothrombotic mechanism and circulatory failure might lead to poor recovery or high
 43 mortality in patients with dyspnic MI.

44

45 *Keywords: Medullary infarction; respiratory dysfunction; neurological profile; lesion*
 46 *topography; arterial pathogenesis.*

47 1. INTRODUCTION

48 Medullary infarction (MI) is an uncommon disorder among patients with cerebral
 49 infarction, and the frequency of MI has been reported as approximate 1-4% in acute
 50 ischemic stroke [1-3]. Respiratory failure plays a crucial role in the prognosis of stroke

51 patients. Occasionally, MI could induce dysfunction of both automatic and voluntary
52 respiration [4, 5] or failure of voluntary respiratory control with preserved automaticity
53 [6, 7]. Little is known about the prevalence, the neurological finding and the
54 radiological topography in MI patients with respiratory disturbance. Here we aimed to
55 elucidate the frequency and the clinicoradiological profile in patients with dyspnic MI.
56

57 **2. PATIENTS AND METHODS**

58 **2.1 Study Patients**

59 We reviewed clinical records and radiological findings of magnetic resonance imaging
60 (MRI) and angiography (MRA) in 2144 consecutive inpatients (1211 men and 933
61 women) with acute ischemic stroke from 2007 to 2013. The clinicoradiological features
62 were examined in MI patients with respiratory dysfunction. The frequency of these
63 patients was estimated among patients with cerebral infarction and MI, respectively.
64 Patients with extensive infarction in the brainstem or the posterior circulation area, and
65 cerebral hernia were excluded from this study. The present study was approved by
66 ethical committee of Toho University Omori Medical Center.

67 **2.2 Radiological Assessment**

68 Brain MRI and MRA was produced by a 1.5-tesla superconducting system. MRI
69 contained diffusion weighted, apparent diffusion coefficient map, T1-weighted,
70 T2-weighted and fluid-attenuated inversion recovery images. Topography of MI was
71 divided into the following 8 areas of the medulla oblongata; the upper, the middle and
72 the lower level on cranio-caudal axis, and the lateral, the medial, the ventral, the
73 tegmental and the dorsal region on transverse axis. Two experienced neurologists and
74 one neuroradiologist reviewed brain MRI and MRA in all patients.

75 **2.3 Clinical Assessment**

76 The Clinical records of all participants were reviewed retrospectively for age, sex, usual
77 cardiovascular disease (CVD) risk factors and vital signs.

78

79 **3. RESULTS**

80 **3.1 Prevalence and Clinical Profile of MI Patients with Respiratory Dysfunction**

81 Among 2144 patients (1211 men and 933 women) with acute ischemic stroke, 95
82 patients (47 men and 48 women) were diagnosed as MI. Six patients (2 men and 4
83 women) developed respiratory dysfunction. The prevalence was 6.3% (4.3% in men and
84 8.3% in women) in MI patients, and 0.3% (0.2 % in men and 0.4% in women) in
85 patients with ischemic stroke.

86 These demographic data are summarized in Table 1. The patient age was ranged from
87 38 to 78 years and the mean age (SD) was 70.0 (22.3) years. The first neurological
88 examination revealed absent pharyngeal reflex and mild to moderate degree of soft
89 palatal palsy in all patients. In addition to respiratory dysfunction, cough syncope,
90 hiccup, circulatory failure, dysphagia, sensory deficits or dysuria was present. Abnormal
91 respiration patterns included hyperventilation in 4 patients, dyspnea in one patient and
92 apnea in one patient. All patients developed respiratory dysfunction during awaking
93 and/or sleeping time at the same day of MI onset.

94 CVD risk analyses revealed hypertension in 5 patients, smoking in two and arrhythmia
95 in one. The prognosis of dyspnic MI was fatal in 2 patients and poor in 2 patients.
96 Remaining two patients had good recovery. One patient was treated with vascular
97 intervention and another patient improved naturally.

98 **3.2 Radiological Profile of MI Patients with Respiratory Dysfunction**

99 Lesion topography is shown in figure 1.

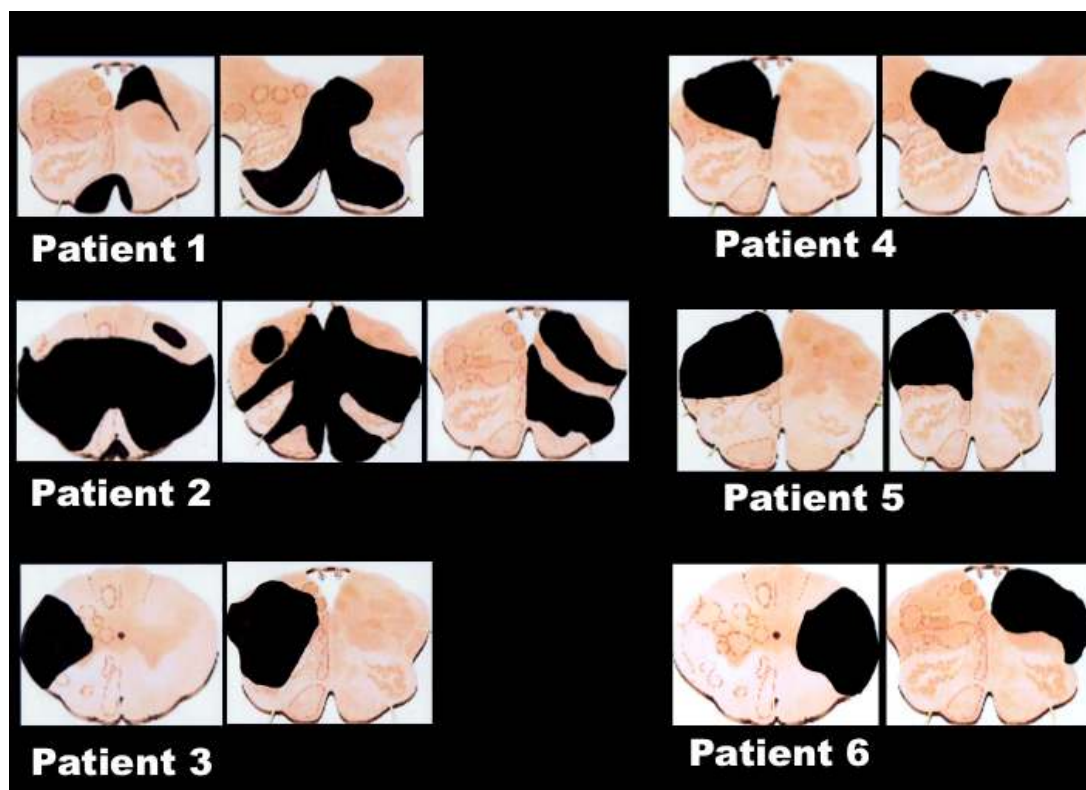


Fig. 1. Schema of lesion topography.

Four patients had unilateral MI and two had bilateral MI. MRI lesion topography were classified to 3 patterns: 1) the bilateral medial and the right tegmental regions in the upper and the middle medulla oblongata, 2) the right-predominant extensive regions in the lower medulla oblongata, and 3) the left lateral and tegmental regions in the lower medulla oblongata. Vascular images disclosed severe degree of atherosclerosis (atherothrombosis) in 3 patients (Fig. 2), dissection of the vertebral artery in 2 patients (Fig. 3) and dural arteriovenous fistula in one patient (Fig. 4).

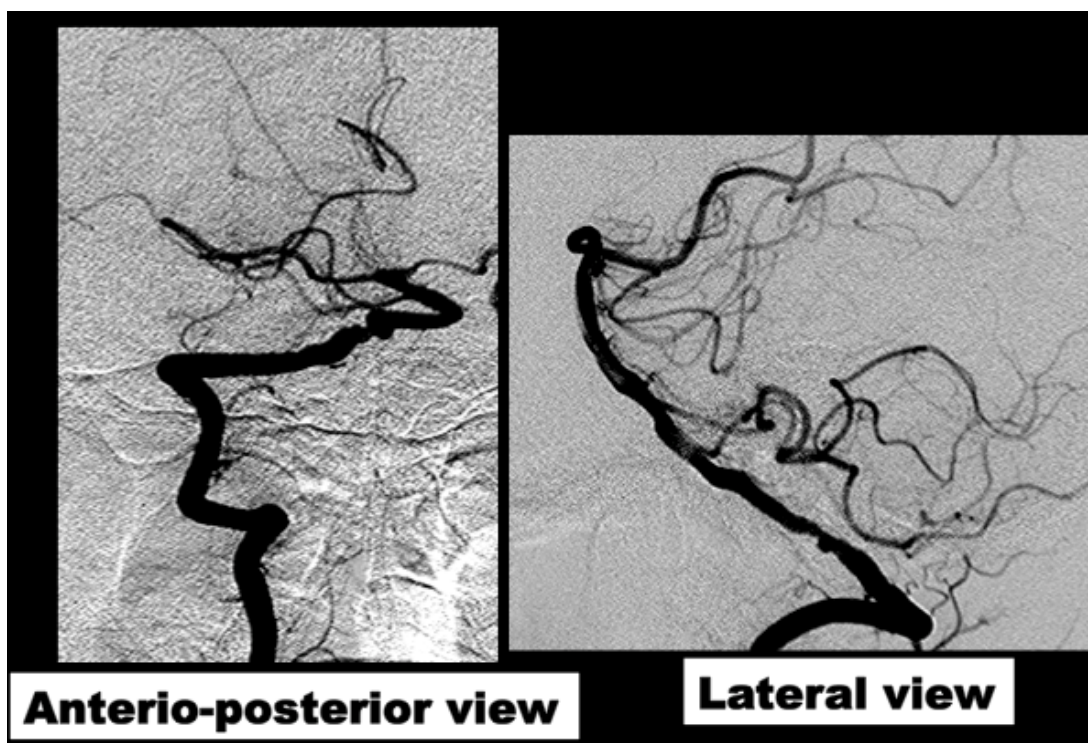


Fig. 2. Cerebral angiogram in Patient 1.

Severe degree of atherosclerotic changes was found in the basilar and vertebral arteries.

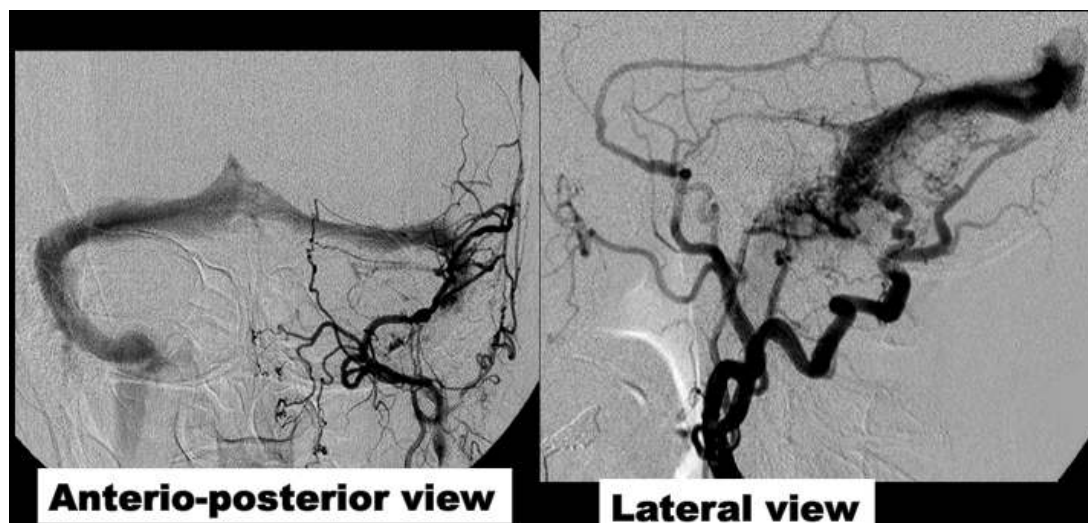
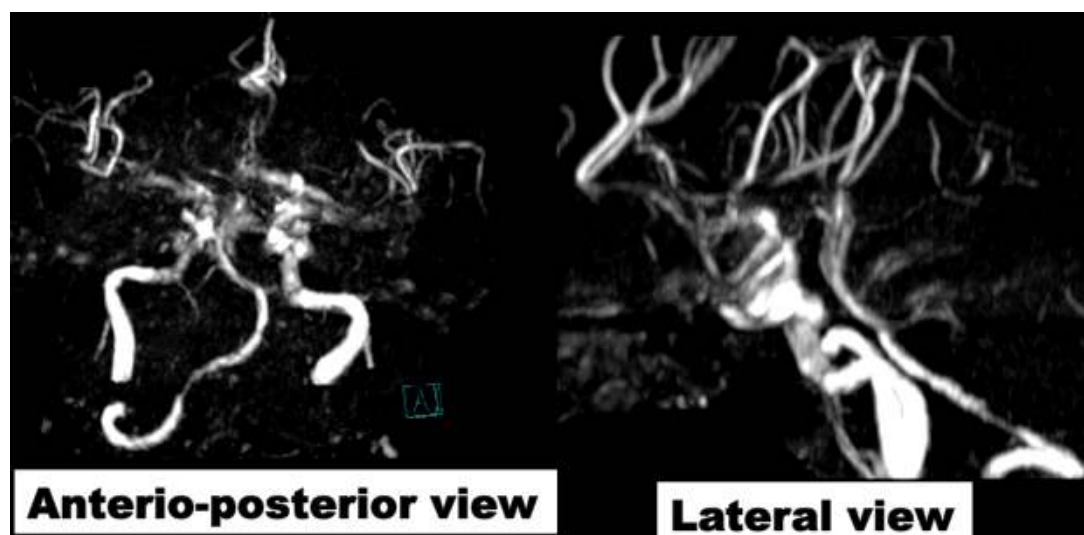


Fig. 3. MRA findings in Patient 3.

Marked stenosis was found in the right vertebral artery, presumably suggesting

116 dissection in the vertebral artery.

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Fig. 4. Cerebral angiogram in Patient 2.

120 Dural arteriovenous fistula was found in the infratentorial region

121

122 **4. DISCUSSION**

123 The present study reported that the prevalence of dyspnic MI was 0.3% in patients with
124 acute ischemic stroke and 6.3% in MI patients. Initial neurological examination showed
125 soft palatal palsy and absent pharyngeal reflex. The neurological profile suggested that
126 cough syncope, hiccup, circulatory failure, bulbar palsy, sensory deficits or dysuria in
127 dyspneic MI patients. The frequency of hypertension was high (83%) on CVD risk
128 factors. Radiological topography of MI disclosed the unilateral side in 4 patients and the
129 bilateral sides in 2 patients. The arterial lesion of dyspnic MI showed atherothrombosis
130 in 3 patients, arterial dissection in 2 patients and dural arteriovenous fistula in one
131 patient. The prognosis was fatal or poor in 4 patients (67%).

132 Kumral et al [8]. described 6 patients with acute respiratory failure due to involvement
133 of the unilateral dorsolateral medulla oblongata among 4500 consecutive inpatients with

134 the first ischemic stroke during 7 years. The prevalence of dyspnic MI was calculated at
 135 0.13% in patients with the first ischemic stroke [8]. The present study indicated that that
 136 was 0.3% in patients with acute ischemic stroke and 6.3% in MI patients.

137 Respiratory dysfunction due to the damage in the medulla oblongata was described in
 138 various diseases, including stroke, poliomyelitis, neoplasm, multiple sclerosis,
 139 syringobulbia, trauma and other causes [9-11]. The anatomical location of the central
 140 ventilatory system has been speculated in the human. Multiple independent respiratory
 141 centers in the brainstem act upon breathing. The respiratory centers are divided into
 142 medullary and pontine centers. The medullary centers comprise 2 groups of cells: 1) a
 143 dorsal group in the nucleus of the solitary tract driving the respiratory system in the
 144 contralateral spinal cord and 2) the ventral respiratory group in the nucleus
 145 retroambiguus situated in the reticular formation around the nucleus ambiguus driving
 146 inspiratory and expiratory neurons by the vagus nerve. The pre-Bötzinger region of the
 147 ventral respiratory group has been hypothesized to be the source of intrinsic pacemaker
 148 activity that drives respiration. These dorsal and ventral groups regulate the respiratory
 149 rhythm. The pontine center is the pneumotaxic center situated in the medial parabrachial
 150 and Kölliker-Fuse nuclei. The pontine center regulates the 2 medullary centers. Besides
 151 its rostro-caudal organization, respiration depends on a parallel system supporting
 152 voluntary, automatic and limbic control of breathing [12-14]. All 3 groups of neurons
 153 are paired bilaterally. Originally, it was thought that bilateral damage was necessary to
 154 induce central hypoventilation because each side seemed to have the ability to
 155 independently drive diaphragmatic activity. However, autopsy-proved unilateral
 156 infarction in the lateral medullary tegmentum demonstrated unequivocally that
 157 unilateral damage can cause the syndrome [15]. In such a case, damage to crossing
 158 fibers connecting the paired medullary nuclei has been proposed as a possible

159 explanation [16]. Respiratory impairment may occur due to involvement of the efferent
 160 pathways from the medullary respiratory centers crossing to the opposite side of the
 161 medulla before descending into the spinal cord [17]. Main previous patients of dyspnic
 162 MI are listed in table 2. Respiratory dysfunction was usually reported in patients with
 163 the unilateral MI, so called Wallenberg's syndrome [8, 9, 15, 18-28]. Such detailed
 164 clinicopathological studies addressed that caudal brainstem stroke involving the dorsal
 165 motor nucleus of the ninth and the tenth cranial nerve, the tractus solitarius and the
 166 medullary reticular formation could trigger central respiratory failure [4, 5, 8, 9, 18-28].
 167 The unilateral lesion topography exhibited the lateral or dorsolateral portion, including
 168 the tegmentum. The lesion side was the left or right without significant laterality or
 169 predominance. The pathogenesis of dyspnic MI has revealed atherothrombosis,
 170 dissection or microembolism in the vertebral artery. The present study showed
 171 additional cause of dural arteriovenous fistula in one patient. The patient age might
 172 depend on the causative lesion of the vertebral artery. In patients with atherosclerotic
 173 changes or microembolism, the onset age was older than 60-70 years. Otherwise, that
 174 was younger at 30-60 years in patients with the vertebral artery dissection compared to
 175 atherothrombotic patients.

176 Respiratory dysfunction generated from a few hours to several days after MI onset. The
 177 most of patients had dyspnea within 5 days of acute phase [8, 9, 15, 18-21, 23-25].
 178 However, the delayed development of central apnea at more than 9 days after MI was
 179 also described in several cases [22, 26-28]. The delayed mechanism of respiratory
 180 dysfunction from 7 days to 3 months post-infarction could contribute to thrombus
 181 spreading, peri-infarctive edema, secondary neuronal degeneration, apoptosis, or
 182 abnormal plasticity involving local synaptic interconnections after MI. Neurological
 183 examination suggested dysphagia or hiccup frequently in previous patients with dyspnic

184 MI, besides the distinct tomography of sensory deficits, Horner's sign and ataxia of
 185 Wallenberg's syndrome [8, 9, 15-28]. The present study disclosed that all patients had
 186 absent pharyngeal reflex and variable degree of soft palatal palsy. The nucleus
 187 ambiguus, the glossopharyngeal and the vagus nerve might be damaged in our patients.
 188 The medullary respiratory center was located around the nucleus ambiguus driving
 189 inspiratory and expiratory neurons by the vagus nerve [12-14]. Therefore, pharyngeal
 190 reflex and paralysis might be crucial and predictive findings for developing respiratory
 191 dysfunction in MI patients. The prognosis was fatal in patients with dyspnic MI even if
 192 mechanical ventilator was used. Two patients died at 1-11 months after MI onset [8, 25].
 193 Two of our patients (25%) died. Patient 1 had 2nd MI at 3 months later. Patient 3
 194 developed recurrent MI at two days after the first MI. In particular, the prognosis was
 195 fatal in those patients who accompanied circulatory changes of blood pressure and heart
 196 rate. Tonic and reflex activity of medullary neurons that mediate sympathetic and
 197 parasympathetic cardiovascular reflexes is affected by respiration, and these vasomotor
 198 centers are located in close proximity to the ventral respiratory group and dorsal
 199 respiratory group. Instability of blood pressure and heart rate has been reported after
 200 lateral medullary infarction in association with central hypoventilation. The respiratory
 201 center seems to exist near the circulatory center and the urinary center in the medulla
 202 oblongata. In general, the mortality of dyspnic MI was higher in patients with the
 203 atherothrombosis compared to microembolism and arterial dissection [8, 25]. The
 204 present and previous patients supported that high frequency of bulbar palsy in patients
 205 with dyspnic MI. Circulatory instability of blood pressure and heart rate might be a fatal
 206 neurological indicator.

207 **5. CONCLUSION**

208 The present study indicated that the prevalence of dyspnic MI was 0.3% in patients with
 209 acute ischemic stroke and 6.3% in MI patients. Neurological examination revealed
 210 cough syncope, hiccup, circulatory instability, bulbar palsy, sensory deficits or dysuria.
 211 Particularly, pharyngeal areflexia and soft palatal palsy was found on initial
 212 examination. These pharyngeal findings might be alerted to development of dyspnea in
 213 MI patients. The frequency of hypertension was highest on CVD risk factors. The
 214 prognosis was fatal in 2 patients (33%). Radiological topography disclosed unilateral
 215 MI in 4 patients and bilateral MI in 2 patients. The pathogenesis of dyspneic MI could
 216 contribute to atherothrombosis, arterial dissection and dural arteriovenous fistula.
 217 Infarctive side and size were not correlated with the prognosis. The atherothrombotic
 218 lesion and circulatory failure could contribute to poor recovery or high mortality in
 219 patients with dyspnic MI.

220 **CONTENT**

221 All authors declare that written informed consent was obtained from all patients for
 222 publication of this study and accompanying images.

223

224 **ETHICAL APPROVAL**

225 The authors have obtained ethical approval from the ethical committee of Toho
 226 University Omori Medical Center.

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Table 1. Clinical profile of MI patients with respiratory dysfunction

Patient	Age	Sex	Arterial lesion	Respiratory patterns	Degree of palatal palsy	Other neurological findings*	Prognosis
1	78 years	female	AT	apnea	mild	hiccup, cough syncope, arrhythmia, circulatory failure	death
2	78 years	female	AVF	dyspnea	mild	sensory deficits below the necks, dysuria	good**
3	38 years	male	AD	hyperventilation	severe	Wallenberg's syndrome, BP instability	death
4	52 years	male	AD	hyperventilation	mild	Wallenberg's syndrome	good
5	88 years	female	AT	hyperventilation	moderate	Wallenberg's syndrome	poor
6	86 years	female	AT	hyperventilation	severe	Wallenberg's syndrome	poor

Abbreviations: AD, arterial dissection; AT, atherothrombosis; AVF, arteriovenous fistula; BP, blood pressure; MI, Medullary infarction.

Patient 1 was reported previously in reference 29. * All patients had absent pharyngeal reflex. ** Intervention treatment.

308 **Table 2. Main previous cases of MI patients with respiratory dysfunction**

309	Authors (reported year)*	Patient number	Lesion side
310	Askenasy (1988) ⁹	1 patient	left
311	Hashimoto (1989) ¹⁸	1 patient	left
312	Bogousslavsky (1990) ¹⁹	2 patients	left (1), right (1)
313	Takehara (1992) ²⁰	1 patient	right
314	Levin (1997) ¹⁵	1 patient	left
315	Iwasaki (2001) ²¹	1 patient	right
316	Oya (2001) ²²	1 patient	right
317	Terao (2004) ²³	1 patient	left
318	Takabatake (2005) ²⁴	1 patient	left
319	Lassman (2005) ²⁵	1 patient	right
320	Arai (2008) ²⁶	2 patients	right (2)
321	Kumral (2011) ⁸	6 patients	left (4) right (2)
322	Mendoza (2013) ²⁷	1 patient	left
323	Sugawara (2014) ²⁸	1 patient	right
324	Present study	6 patients	left (3), right (1), bilateral (2)

325 *Reference number.

326 Abbreviations: MI, Medullary infarction.