Title. Neurologic Deficit Following Total Aortic Arch Replacement using Antegrade Cerebral Perfusion

Running head. Neurologic Deficit Following Total Aortic Arch Replacement

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Abstract

Background: Recent advances in contrast-enhanced computed tomography have allowed for the accurate imaging of the atherothrombotic aorta.

Methods: A group of 198 consecutive patients undergoing isolated total aortic arch replacement using antegrade cerebral perfusion were analyzed for the risk factors of neurologic deficit. Using computed tomography, atherothrombotic lesions (defined as extensive intimal thickening exceeding 4 mm) were identified in the proximal aorta (the ascending aorta or aortic arch) in 26.2% of cases and in the distal aorta in 34.9% of cases.

Results: Permanent neurologic deficits occurred in 11.1% (including non-disabling stroke confirmed by imaging) and transient neurologic deficits (such as delirium) in 8.1% of patients. A univariate analysis identified proximal atherothrombotic aorta (p=0.0057), distal atherothrombotic aorta (p=0.032), and retrograde systemic perfusion from the femoral artery in the presence of distal atherothrombotic aorta (p=0.0022) as risk factors for neurologic deficits. A multivariate logistic regression analysis identified atherothrombotic proximal aorta (odds ratio, 2.5) as the independent risk factor. The presence of carotid stenosis did not affect the rate of neurologic deficit. Intracranial hemorrhagic lesions were found in 23% of permanent neurologic deficit cases.

Conclusions: Strategies based on the full assessment of the whole aortic morphology appear to be mandatory in order to minimize the risk of neurologic deficit. Retrograde perfusion in the presence of a distal atherothrombotic lesion should be avoided whenever possible. Anticoagulation therapy should be performed very carefully to avoid intracranial hemorrhagic changes.

Keywords: aortic arch replacement, stroke, neurologic deficit

Word count: 234 words

Introduction

With refinements in operative techniques using brain protection including antegrade cerebral perfusion (ACP), total aortic arch replacement can now achieve acceptable surgical outcomes [1, 2]. Nevertheless, postoperative neurologic deficits, including permanent neurologic deficits (PNDs) and transient neurologic deficits (TNDs) are still associated with significant morbidity [3, 4]. PNDs include stroke with evidence of morphological changes, while TNDs include short-term global neurocognitive decline or transient focal deficit without morphological changes. Previous reports have shown that a correlation exists between the severity of the neurologic deficits and the duration of the brain circulatory arrest during aortic surgery [5]. The use of ACP, however, has enabled a reduction in the cerebral ischemic time. Recent reports have suggested that a significant number of PND and TND cases may be associated with multiple atheroembolization [6]. Atheromatous plaque in the proximal aorta detected by trans-esophageal echocardiography (TEE) was reported to be a significant risk factor for stroke after cardiac surgery [7]. Similarly, recent advances in contrast-enhanced computed tomography (CT) have allowed for the accurate preoperative imaging of the atherothrombotic aorta, which is thought to be a source of emboli [8, 9]. Furthermore, retrograde systemic perfusion from

femoral arteries has been thought to carry a risk of retrograde embolic stroke due to frequent atherosclerotic changes in the abdominal aorta and iliac arteries [10].

The purpose of the present study was to evaluate the predictors of neurologic deficit after total aortic arch replacement using ACP in order to prevent such deficits. In addition, details of neurologic deficit cases were assessed in order to identify specific points of consideration to prevent deficits.

Patients and methods

Inclusion and exclusion criteria

From 2008 to 2017, 744 open operative repairs of the thoracic aorta were performed at Nagoya University Hospital. Isolated total arch replacement procedures via median sternotomy were included in the study. To satisfy the definition of total arch replacement, the aortic arch area between the brachiocephalic artery and the left subclavian artery were to be replaced and the arch vessels reconstructed. Subtotal aortic arch replacement were not included. Aortic arch procedures via thoracotomy were not included. Median sternotomy with additional partial thoracotomy (L-incision) was regarded as a median sternotomy approach, and such cases were included [11]. Total arch replacement with the concomitant use of the frozen elephant trunk technique (n=36) was included. In contrast, off-pump arch vessel debranching procedure with subsequent thoracic endovascular aortic repair (TEVAR) [12] was not included. Total aortic arch replacement for urgent repair of acute aortic dissection (n=23) and cases with concomitant cardiac procedures other than coronary artery bypass grafting (CABG) (n=37) were also excluded.

After applying the exclusion criteria, 198 patients who underwent isolated total arch replacement via median sternotomy, excluding acute dissection cases, were included in the

present study. The records of these patients were retrospectively reviewed. The present retrospective review study was approved by the Institutional Review Board (IRB 655-2); the need for individual consent was waived. The indication of aortic arch replacement was based on the standard guidelines and was at the discretion of the multidisciplinary team.

Neurologic imaging and aortic morphology evaluation

For the pre-operative assessment of aortic arch operations, all patients in the study period routinely underwent neurologic imaging, along with the morphology evaluation of the whole aorta using CT prior to the operation. Neurologic imaging included routine head and neck magnetic resonance angiography (MRA) with simultaneous brain magnetic resonance imaging (MRI) scans. If required, carotid duplex and/or contrast-enhanced brain CT were performed as complementary tests to assess the degree of stenosis. Carotid stenosis was defined as the presence of linear stenosis exceeding 70% based on the North American Symptomatic Carotid Endarterectomy (NASCET) method or its equivalent degree of stenosis [13].

The morphologies of each part of the aorta were evaluated separately in the ascending aorta, aortic arch, descending aorta, abdominal aorta and iliac arteries. We have been using the grading protocol of aortic atherosclerotic morphologies based on contrast enhanced CT as

follows [8, 14]: Grade 1, no intimal thickening; Grade 2, mild intimal thickening <2 mm; Grade 3, moderate intimal thickening (2 to <4 mm); Grade 4, extensive intimal thickening ≥4 mm; Grade 5, mobile-looking, ulcerated or protruding atheroma (Figure 1). This grading is based on the widely used Katz's grading of aortic morphology evaluated by TEE [7]. Grade 4 or 5 lesions were classified as atherothrombotic lesions (so called "shaggy aorta") [14, 15].

Surgical protocols

Since 2007, we have introduced a brain protection protocol with the routine use of ACP with selective perfusion cannulas in cases of aortic arch replacement. This is to ensure the margin of safety of brain ischemic time [1]. Because of this policy, ACP was always applied for brain protection in the present study period.

The operative techniques of total aortic arch replacement using ACP have been well documented [16,17,18]. Our current routine for performing total arch replacement is as follows: The first choice of arterial cannulation site was the ascending aorta however it may be modified. The cannulation site was finally chosen based on the the morphology information obtained by CT and epi-aortic echography, the location of the aneurysm, and the location of the dissected vessels. In redo-sternotomy cases, other cannulation sites (femoral artery or

axillary artery) are favored to ensure the safety during redo-sternotomy. Overall, femoral artery cannulation and retrograde systemic perfusion was performed in 17.7% of the patients. Following the establishment of CPB and core cooling, after the pharyngeal temperature decreases to 25 °C, circulatory arrest is induced, and the aortic arch is opened. Balloon-tipped ACP cannulas are then inserted into the brachiocephalic artery, the left common carotid artery and the left subclavian artery. If atheromatous changes are remarkable at the orifice of the arch vessels, the arch vessels may be transected 1 cm above the orifice before the insertion of ACP cannulas. Antegrade cerebral perfusion flow is maintained at 15 mL/kg/min using an independent roller pump, and the mean pressure is maintained between 30 and 40 mmHg (measured by the radial artery pressure). The anterior cerebral regional oxygen saturation (rSO_2) is continuously monitored [19]. A decrease in the rSO_2, especially more than 15% from the baseline, is regarded as a situation requiring caution. In such cases, adjusting the cannula position as well as flow adjustment is attempted. Open distal anastomosis is performed during hypothermic cardiac arrest of the lower body [18]. The proximal aorta and arch vessels are then individually reconstructed using a branched graft. As a technical modification of ACP, for cases with a very atheromatous aortic arch, ACP is started before systemic perfusion has been

fully initiated. This technique (isolation technique n=16, 8.1%) is meant to isolate the brain circulation from systemic perfusion in order to prevent embolism from the aorta [20, 21].

Definition of neurologic deficits and morbidities

Neurologic deficit included TND and PND of the brain. Spinal cord ischemia was not considered neurologic deficit in the present study. More specifically, TNDs included short-term clinical manifestations of neurocognitive decline, such as delayed awakening, confusion and delirium. In addition, TND also included transient focal deficits that recovered within 24 hours without morphological changes (transient ischemic attack; TIA). In contrast, PND (stroke) was defined as the new onset of focal neurologic injury or global dysfunction, with morphological correlates in neurologic imaging. PND was further divided into disabling and non-disabling stroke. An increase in the modified Rankin score of ≥2 points generally indicates the occurrence of a significant disabling event [22] and was used to divide PND into disabling and non-disabling stoke. Unless otherwise mentioned, definitions of preoperative risks and postoperative outcomes were based on the Japan Adult Cardiovascular Surgery Database (JACVSD) protocols [23].

Statistical analyses

Statistical analyses were performed based on our previous report [11] using the JMP version 13 software program (SAS Institute, Inc., Cary, NC, USA). For simple comparisons, the patient population was divided in two groups: those with post-operative neurological deficit and those without deficit. For the risk analysis, a logistic regression analysis was performed. For the multivariate analysis, a logistic regression model was developed using a forward stepwise variable selection method.

Results

Pre-operative and intraoperative profiles and aortic morphology

A total of 198 patients were included in the study. The average age of the patients was 68.5 ± 9.7 years with male predominance. An abbreviated preoperative risk profile for the study population is summarized in Table 1. Of note, 8.1% of patients had carotid artery stenotic lesions. Overall, atherothrombotic lesion (Grade 4 or 5) was present in 12.6% at the ascending aorta, 25.8% at the aortic arch, 29.8% at the descending aorta and 25.8% at the abdominal aorta.

The intraoperative variables are listed in Table 2. Regarding the systemic perfusion strategy, 35 (17.7%) patients received retrograde systemic perfusion from the femoral artery. The remaining 163 patients received antegrade perfusion from the ascending aorta (n=137), aortic arch (n=9) or axillary artery (n=17). In particular, 6.6% of the patients received such retrograde perfusion in the presence of a distal atherothrombotic aorta.

Postoperative outcomes and details of neurologic deficits

The outcomes in the present study population were an operative mortality rate of 4.5%. The specific morbidity rates are also presented in Table 3.

PND occurred in 11.1% (n=22) of cases, including 15 cases of disabling stroke (7.6% of all cases, 39.5% of all neurologic deficit cases). TND occurred in 8.0% (n=16) of cases. In total, neurologic deficit occurred in 19.1% (n=38) of cases. Of the 22 cases of PND, intracranial hemorrhagic lesions were found in 5 (22.7% of PND cases), and 3 of the 5 were confirmed to be hemorrhagic infarction (infarction complicated with subsequent hemorrhagic transformation). All cases with intracranial hemorrhage (n=5) had received anticoagulation therapy prior to the occurrence of hemorrhaging for various reasons (previous mechanical heart valve replacement, n=2; atrial fibrillation, n=1; circulatory support, n=2) (Figure 2). In particular, two cases were receiving extracorporeal membrane oxygenation (ECMO) as circulatory support. In the confirmed primary infarction cases (n=20), multiple infarcted lesions were found in 14 cases (70% of 20 infarction cases). There were no cases of watershed-type infarction, which is usually thought to be due to hemodynamic hypoperfusion.

Risk factor analysis of predicting neurologic deficits

Comparison of the patients with and without neurologic deficit are described in Tables 1 and 2. According to the univariate analysis (listed in Table 4), atherothrombotic lesion in the proximal aorta (odds ratio [OR], 2.89, 95% confidence interval [CI], 1.38-6.07) and such

lesions in the distal aorta (OR 2.20, 95% CI, 1.07-4.51) were found to be the risk factors of the neurologic deficit. In addition, retrograde perfusion in the presence of a distal atherothrombotic lesion was also a strong risk factor for deficit (OR, 4.1, 95% CI, 1.29-13.0). In contrast, carotid artery stenosis was not regarded as a risk factor of neurologic deficit. The type of aneurysm (chronic dissection) also did not affect the rate of neurologic deficit. The risk analysis failed to show any apparent benefit of the isolation technique for preventing embolic neurologic deficit.

According to the multivariate logistic regression analysis, the risk factors model for predicting neurologic deficits (p=0.0058) included proximal atherothrombotic aorta (OR, 2.48, 95% CI, 1.14-5.35) and retrograde perfusion thorough the distal atherothrombotic aorta (OR, 2.81, 95% CI, 0.83-9.46).

Discussion

The present study indicated that atherothrombotic lesions were not uncommon in patients undergoing aortic arch replacement[8, 15]. Not only atherothrombotic lesion at the proximal aorta but also those at the distal aorta were significant predictors of the occurrence of neurologic deficit following total aortic arch replacement. In addition, retrograde perfusion from the femoral vessels in the presence of an atherothrombotic lesion at the descending or abdominal aorta also carried a strong risk of neurologic deficit. In contrast, retrograde systemic perfusion itself was not regarded as a risk factor. Based on these results, retrograde perfusion in the presence of a distal "shaggy" lesion should be avoided whenever possible. Even if perfusion via the ascending aorta is technically difficult (e.g. redo-sternotomy case), antegrade perfusion could be achieved via the axillary artery.

In addition, the present study failed to show any benefit of the isolation technique (ACP established first and cerebral perfusion isolated prior to systemic perfusion) in cases with a "shaggy" aortic arch. However, it is practically difficult to draw a definitive conclusion because of the small number of cases treated with the technique. Filter-based embolic protection devices have been reported to be effective for reducing stroke during trans-catheter aortic valve implantation [24]. In the future, such novel methods may be feasible options for preventing

stroke during aortic arch operations. Further studies are needed to establish a more effective method of preventing embolic neurological deficit in such high-risk patients.

In contrast, provided the brain was adequately perfused using ACP, carotid artery stenotic lesions did not carry a risk of neurologic deficit. These results implied that ACP under moderate hypothermia with continuous monitoring of the perfusion pressure and rSO_2 allowed for safe perfusion adjustment, even in cases with such stenotic lesions.

In addition, the present study has also shown that intracranial hemorrhaging was not an uncommon complication (n=5, 22.7% in PND). In general, hemorrhagic transformation is a known consequence of acute ischemic stroke. Disruption of the blood brain barrier following ischemia and reperfusion injury is thought to be a principal mechanism [25]. Large infarction, reduced platelet counts and hyperglycemia along with thrombolysis or anti-coagulation therapy are known risk factors of hemorrhagic transformation. Furthermore, intracranial hemorrhaging is a recognized complication of ECMO [26]. Such situations are not rare following aortic arch replacement. Extensively strict control of anticoagulation therapy is therefore mandatory in such post-operative stroke patients, not following routine protocols.

However, a potential limitation associated with the present study warrants mention. The percentage of neurologic deficit, represented by the sum of the percentage of PND and TND,

was higher in our study than in previous studies [8, 16, 23]. As possible explanations, PND in the present study included not only disabling stroke but also non-disabling stroke. Non-disabling stroke is a new lesion found on neurologic imaging without significant accompanying symptoms. The rate of non-disabling stroke therefore depends on the frequency of preforming neurologic imaging. In our protocol, patients suspected of having even a slight neurologic deficit were always evaluated by the specialist neurologist immediately. Subsequently, imaging evaluations, including MRI, were often performed with a low threshold. A similar evaluation protocol was applied for TND. It has been suggested that inter-observer biases exist in the detection of TND, and the rate of TND, especially the rate of delirium, has been generally underreported [23]. These circumstances may result in differences in the rate of neurologic deficit.

Overall, the results of the present study may help clinicians optimize the risk evaluation and perioperative clinical management of patients undergoing aortic arch surgery.

Conclusions

Strategies based on the full assessment of the whole aortic morphology and objective CT grading appear to be mandatory in order to minimize the risk of embolic neurologic deficits in

total aortic arch replacement. Retrograde perfusion in the presence of a distal atherothrombotic lesion should be avoided whenever possible. Intracranial hemorrhage is not rare, suggesting that anticoagulation therapy should be performed very carefully in post-operative patients.

Disclosures

The authors have no conflicts of interest regarding this study.

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Table 1. Baseline characteristics of the patients

	overall cohort n=198	with neurologic deficit n=38	without neurologic deficit n=160	*P*-value
Mean age, years	68.5±9.7	70.6±9.9	68.8±9.7	0.29
Male gender	161 (81.3%)	33 (86.8%)	128 (80.0%)	0.48
Chronic lung disease (moderate to severe)	20 (10.1%)	4 (10.5%)	16 (10.0%)	1.00
Renal dysfunction	10 (5.1%)	3 (7.9%)	7 (4.4%)	0.41
History of CVA	22 (11.1%)	5 (13.2%)	17 (10.6%)	0.77
Carotid stenosis	16 (8.1%)	2 (5.3%)	13 (8.8%) (bilateral n=1)	0.74
PAD	86 (43.4%)	16 (42.1%)	70 (43.8%)	1.00
Impaired LV function, EF<50%	13 (6.6%)	1 (2.6%)	12 (7.5%)	0.47
EF	64.7±8.7	66.7±7.6	64.3±8.9	0.09

presence of AAA	31 (15.7%)	7 (18.4%)	24 (15.0%)	0.62
History of cardiac surgery	44 (22.2%)	7 (18.4%)	37 (23.1%)	0.67
Aneurysm type: chronic dissection	40 (20.3%)	4 (10.5%)	36 (22.6%)	0.12
Logistic Euroscore	21.6±14.2	21.8±11.1	21.6±14.9	0.93
Euroscore II	5.1±4.8	4.6±0.6	5.2±0.4	0.37
Atherosclerosis Grade				
Ascending aorta Grade 1, 2, 3, 4, 5	70, 80, 25, 16, 7 (35.3%, 40.4%, 12.6%, 8.1%, 3.5%)	9, 13, 7, 8, 1 (23.7%, 34.2%, 18.4%, 21.0%, 2.6%)	61, 67, 18, 8, 6 (38.1%, 41.8%, 11.2%, 5.0%, 3.7%)	0.014
Aortic arch Grade 1, 2, 3, 4, 5	29, 57, 61, 24, 27	6, 5, 10, 9, 8 (15.8%,	23, 52, 51, 15, 19 (14.4%,	0.02

	(14.7%, 28.8%, 30.8%, 12.1%, 13.6%)	13.2%, 26.3%, 23.7%, 21.1%)	32.5%, 31.8%, 9.4%, 11.8%)	
Descending aorta Grade 1, 2, 3, 4, 5	28, 62, 49, 30, 29 (14.1%, 31.3%, 24.8%, 15.1%, 14.7%)	5, 9, 7, 9, 8 (13.2%, 23.7%, 18.4%, 23.7%, 21.1%)	23, 53, 42, 21, 21 (14.4%, 33.1%, 26.2%, 13.1%, 13.1%)	0.26
Abdominal aorta	32, 74, 35, 38, 21 (16.1%, 37.4%, 17.7%, 18.2%, 10.6%)	4, 13, 5, 12, 4 (10.5%, 34.2%, 13.2%, 31.6%, 10.5%)	28, 61, 30, 24, 17 (17.5%, 38.1%, 18.7%, 15.0%, 10.6%)	0.21
Proximal atherothrombotic lesion	52 (26.2%)	17 (44.7%)	35 (21.8%)	0.007

Distal atherothrombotic lesion	69 (34.9%)	19 (50.0%)	50 (31.2%)	0.037

BMI, body mass index; CVA, cerebrovascular accident; EF, ejection fraction; LV, left ventricle, PAD, peripheral arterial disease.

Table 2. Intraoperative variables

	overall cohort	**with neurological deficit** n=38	**without neurological deficit** n=160	***P*-value**
Urgent operation	9 (4.5%)	3 (7.9%)	6 (3.75%)	0.378
Additional thoracotomy (L incision)	21 (10.6%)	7 (18.4%)	14 (8.7%)	0.317
Concomitant CABG	19 (9.6%)	5 (13.2%)	14 (8.8%)	0.37
Perfusion time, minutes	253.1±65.6	270.5±85.2	249.0±59.6	0.14
Myocardial ischemic time, minutes	133.5±42.2	127.3±45.7	133.0±41.3	0.34

Minimum body temperature (℃)	25.1±1.8	24.8±1.9	25.2±1.8	0.27
Retrograde systemic perfusion	35 (17.7%)	10 (26.3%)	25 (15.6%)	0.15
Retrograde systemic perfusion through the atherothrombotic aorta	13 (6.6%)	6 (15.8%)	7 (4.4%)	0.021
Isolation technique used	16 (8.1%)	5 (13.2%)	11 (6.9%)	0.20

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass.

Table 3. The postoperative outcomes

Operative mortality	9 (4.5%)
Reoperation for bleeding	14 (7.0%)
Renal failure	8 (4.0%)
De novo hemodialysis	5 (2.6%)
myocardial infarction	4 (2.0%)
Requirement of circulatory support	8 (4.0%)
Atrial fibrillation	75 (37.9%)
Mediastinitis	3 (1.5%)
Prolonged ventilation (>72 h)	59 (30.0%)
Tracheostomy	8 (4%)
PND	22 (11.1%)
disabling stroke	15 (7.5%)
TND	16 (8.1%)

Length of stay ICU, days	6.7 ± 7.8 (median, 4)
Compromised ADLs	21 (10.6%)

ADLs, activities of daily living; ICU, intensive-care unit; JACVSD, Japan Adult Cardiovascular Surgery Database; PND, permanent neurologic deficit; TND, transient neurologic deficit.

Compromised ADLs: a modified Rankin scale score of ≥4 (unable to walk without assistance) at the time of discharge.

Table 4. Analyses of risk factors for predicting neurologic deficits

	Univariate		Multivariate	
Characteristic	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
≥70 years of age	1.31 (0.64-2.67)	0.46		
Male gender	1.52 (0.63-3.62)	0.31		
History of CVA	1.21 (0.53-2.78)	0.66		
Carotid stenosis	1.72 (0.38-7.94)	0.45		
PAD	0.93 (0.53-1.69)	0.85		
Perfusion time	1.0046 (1.00-1.01)	0.073		
Proximal aorta atherothrombotic lesion	2.89 (1.38-6.07)	0.0057	2.48 (1.14-5.35)	0.022
Distal aorta atherothrombotic lesion	2.20 (1.07-4.51)	0.032		

Retrograde perfusion through atherothrombotic distal aorta lesion		2.81 (0.83-9.46)	0.096
	4.1 (1.29-13.0)		0.022
Retrograde perfusion	1.93 (0.83-4.5)		0.13
Isolation technique used	2.05 (0.67-6.3)		0.22
Aneurysm type: chronic dissection	0.46 (0.17-1.23)		0.12

CI, confidence interval; CVA, cerebrovascular accident; OR, odds ratio; PAD, peripheral arterial disease.

Figure legends

Figure 1. Example of the morphology assessment of the atherosclerotic aorta. Contrast-enhanced computed tomography demonstrated a protruding, mobile-looking atheroma plaque in the aortic arch (Grade 5).

Figure 2. Computed tomography demonstrated bilateral multiple embolic infarctions in the posterior circulation territory (a). Computed tomography two weeks later in the same patient showed hemorrhagic changes of infarction. This patient was on anticoagulation therapy because of a pre-existing mechanical mitral valve (b).

Figure1

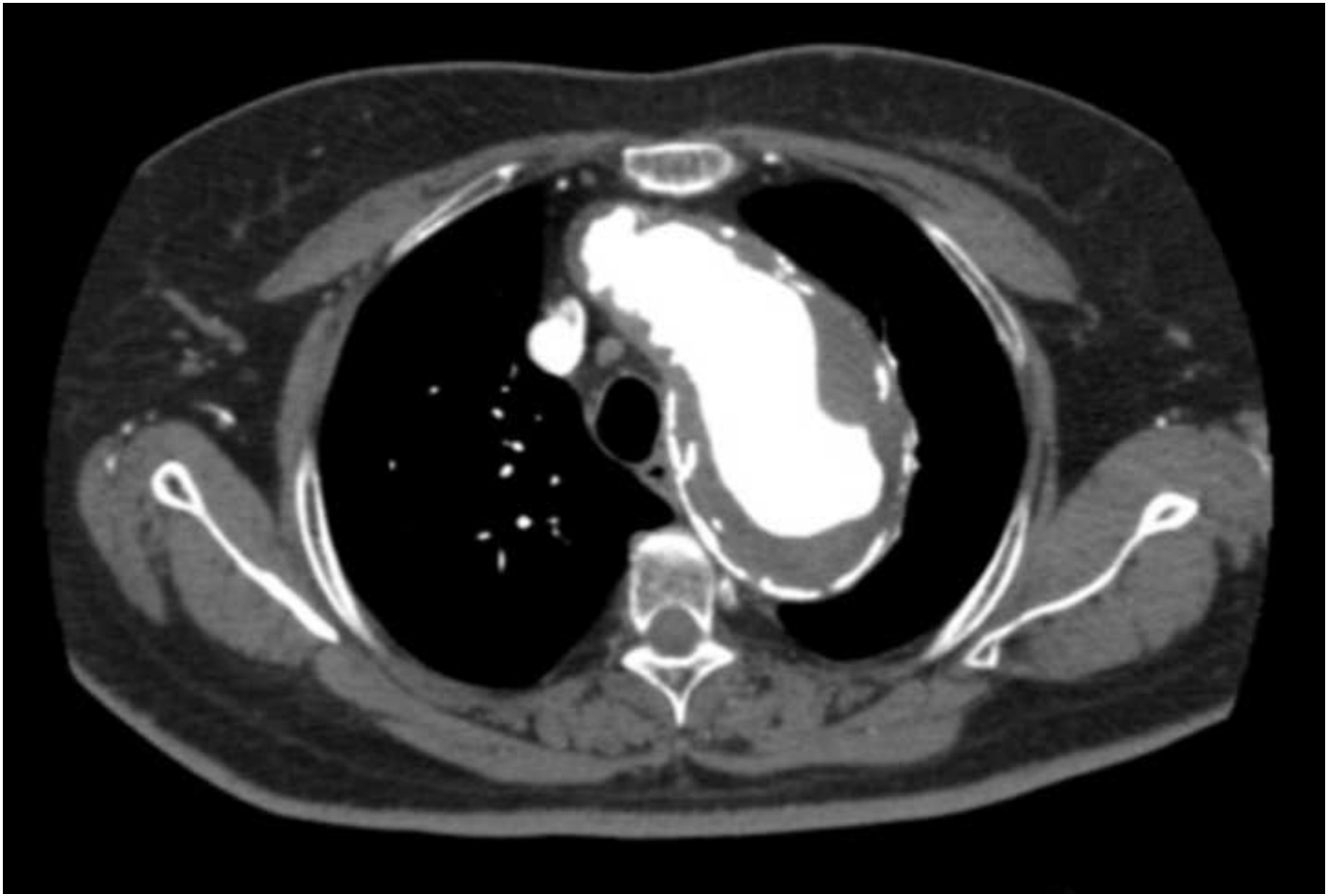

Figure2a

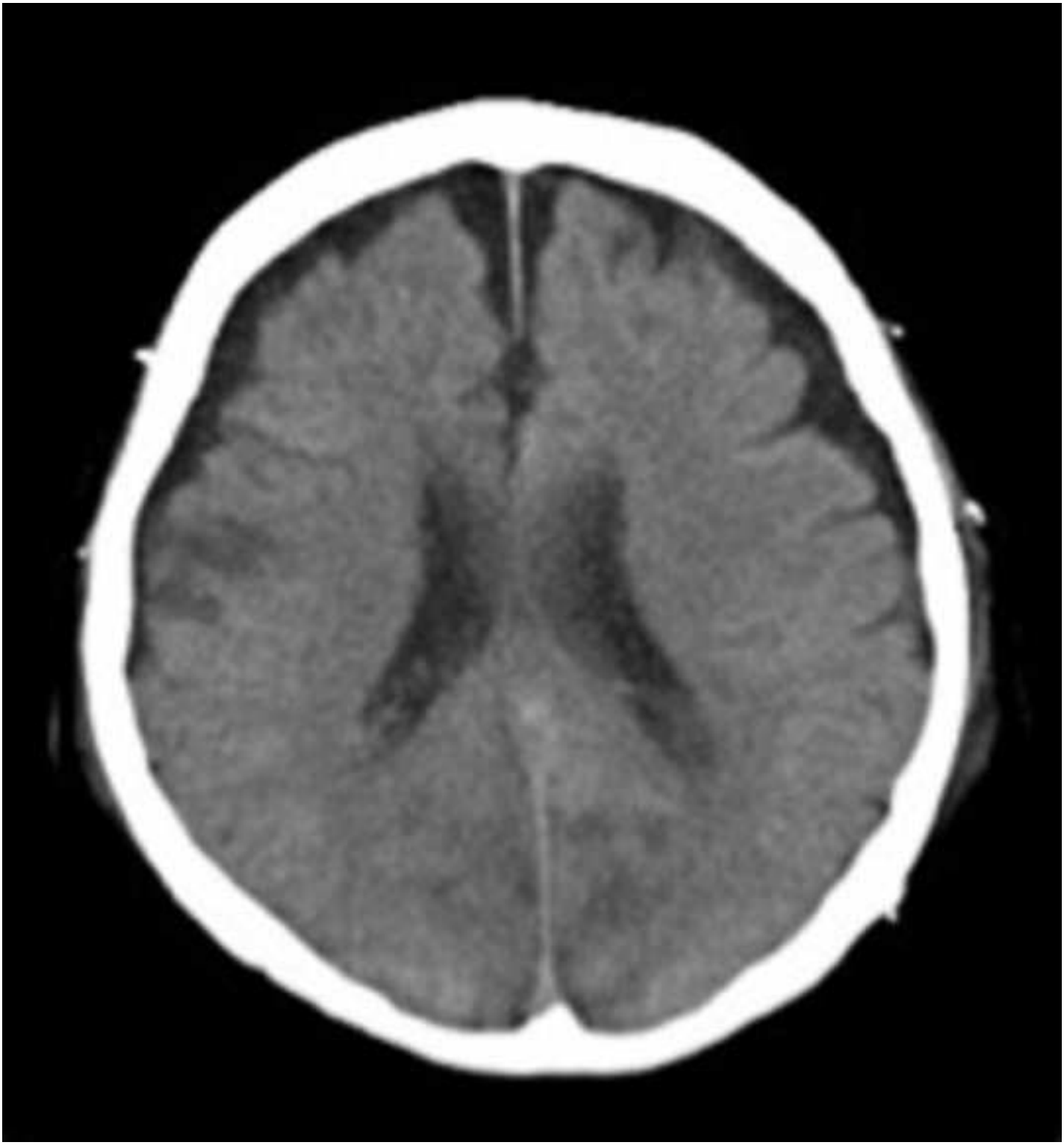

Figure2b