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# Sonolysis in Prevention of Brain Infarction During Cardiac Surgery (SONORESCUE)

## Randomized, Controlled Trial

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**Abstract:** Here, we examined whether intraoperative sonolysis can alter the risk of new ischemic lesions in the insolated brain artery territory during coronary artery bypass grafting (CABG) or valve surgery.

Silent brain ischemic lesions could be detected in as many as two-thirds of patients after CABG or valve surgery.

Patients indicated for CABG or valve surgery were allocated randomly to sonolysis (60 patients, 37 males; mean age, 65.3 years) of the right middle cerebral artery (MCA) during cardiac surgery and control group (60 patients, 37 males; mean age, 65.3 years). Neurologic examination, cognitive function tests, and brain magnetic resonance imaging (MRI) were conducted before intervention as well as 24 to 72 hours and 30 days after surgery.

New ischemic lesions on control diffusion-weighted MRI in the insolated MCA territory  $\geq 0.5$  mL were significantly less frequent in the sonolysis group than in the control group (13.3% vs 26.7%,  $P = 0.109$ ). The sonolysis group exhibited significantly reduced median volume of new brain ischemic lesions ( $P = 0.026$ ). Stenosis of the internal carotid artery  $\geq 50\%$  and smoking were independent predictors of new brain

ischemic lesions  $\geq 0.5$  mL (odds ratio = 5.685 [1.272–25.409],  $P = 0.023$  and 4.698 [1.092–20.208],  $P = 0.038$ , respectively). Stroke or transient ischemic attack occurred only in 2 control patients ( $P = 0.496$ ). No significant differences were found in scores for post-intervention cognitive tests ( $P > 0.05$ ).

This study provides class-II evidence that sonolysis during CABG or valve surgery reduces the risk of larger, new ischemic lesions in the brain.

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**Abbreviations:** ACE-R = Addenbrooke's Cognitive Examination Revised, CABG = coronary artery bypass grafting, CI = confidence interval, DWI = diffusion-weighted imaging, DW-MRI = diffusion-weighted-magnetic resonance imaging, EPI = echo planar imaging, FLAIR = fluid-attenuated inversion recovery, FOV = field of view, ICA = internal carotid artery, MCA = middle cerebral artery, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, OR = odds ratio, SONOBUSTER = Sonolysis in Prevention of Brain Infarctions during Carotid Stenting and Carotid Endarterectomy, SONORESCUE = Sonolysis in Prevention of Brain Infarction during Cardiac Surgery, SYNTAX = Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery, TIA = transient ischemic attack, TIC = thermal index for cranial bone.

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## INTRODUCTION

Cardiac surgery is associated with a significant risk of ischemic stroke and impairment of cognitive function.<sup>1–7</sup> Studies have shown that the risk of stroke after cardiac surgery is 1.3% to 3.6%.<sup>1–3</sup> Microemboli can cause small silent or even clinically manifest brain ischemic lesions with a high risk of cognitive impairment after cardiac surgery that can be detected in  $\leq 88\%$  of patients.<sup>4–7</sup> Slight brain ischemic lesion can be detected using diffusion-weighted-magnetic resonance imaging (DW-MRI) in  $\leq 61\%$  of patients after coronary artery bypass grafting (CABG) or valve surgery.<sup>8</sup>

Sonolysis is a new method for acceleration of artery recanalization. Sonolysis has been shown to be efficacious for treatment of acute ischemic stroke.<sup>9</sup> Animal studies (in vitro and in vivo) undertaken as early as the 1970s reported that ultrasound intensity of  $0.2 \pm 2.0 \text{ W/cm}^2$  at 20 kHz to 2 MHz can accelerate thrombus dissolution.<sup>10–14</sup> More recently, several randomized control trials and case-control studies have demonstrated improved clinical outcome using a diagnostic 2-MHz frequency and maximal diagnostic intensity ( $\approx 1.2 \text{ W/cm}^2$ ) in patients with ischemic stroke owing to middle cerebral artery (MCA) occlusion.<sup>15–18</sup> Underlying mechanisms for

thrombus dissolution are incompletely understood, but they may include acceleration of enzymatic fibrinolysis<sup>19</sup> and mechanical effects such as acoustic radiation force and acoustic cavitation.<sup>20</sup>

The primary aim of this prospective, randomized study was to test the efficacy of sonolysis for reducing the risk of asymptomatic and symptomatic brain ischemic lesions in patients undergoing CABG or valve surgery. We also assessed the effects of sonolysis on cognitive function, morbidity, and mortality 30 days after surgery.

## METHODS

### Ethical Approval of the Study Protocol

The present study was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 2004 and 2008) and approved by the local ethics committee (MZ12-FNO). All patients provided written informed consent before study enrollment. The study is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT01591018) and at The Research and Development and Innovation Information System of the Czech Republic ([www.is-vav.cz/projectDetail.do?rowId=NT13498](http://www.is-vav.cz/projectDetail.do?rowId=NT13498)).

### Patients

Inclusion criteria were: indication for elective CABG or valve surgery with extracorporeal circulation; age 40 to 90 years; temporal bone window sufficient for transcranial Doppler ultrasound with detectable blood flow in the MCA; functional independence (modified Rankin score 0–2 points).

Exclusion criteria were: contraindication for MRI examination (pacemaker, implanted metal material, claustrophobia); emergency surgery; acute myocardial infarction; combined cardiac surgery; combined cardiac surgery and carotid surgery.

Consecutive patients were enrolled during 28 consecutive months (September 2012 to December 2014). Patients were assigned to the sonolysis group or control group by computer-generated 1:1 randomization.

### Cardiac Surgery

CABG and valve surgery were carried out using standard anesthetic and surgical methods by experienced surgeons with >200 CABG or valve surgeries. Surgeons were blinded to treatment groups. For general anesthesia, a combination of sevoflurane, oxygen/air, and sufentanil (Sufenta<sup>TM</sup>; Janssen Pharmaceutica NV, Beerse, Belgium) was used. In CABG patients, the left mammary artery and/or saphenous grafts were harvested using standardized methods.<sup>21</sup> Endoscopic harvesting was preferred for venous grafts.

All patients underwent a median sternotomy and cardiopulmonary bypass in normothermia using nonpulsatile pump flow of 2.4 L/m<sup>2</sup> per minute. Anticoagulation was adjusted at an activated clotting time of >400 s. Cardiopulmonary bypass was established by aortic and single venous cannulation in CABG and aortic-valve procedures. Aortic and bicaval venous cannulation was used for procedures involving the mitral valve and tricuspid valve. Cannulation of the aorta was carried out in an area free from palpable plaques. Cardiac arrest was induced by cold blood cardioplegia using a standardized method.<sup>22</sup> Aortic side clamping was done to fashion proximal venous anastomoses. After completing all anastomoses, patients were weaned from the extracorporeal circulation and cannulae were removed. After decannulation, protamine hydrochloride (Protamin Valeant; ICN Switzerland AB, Biersfelden, Switzerland) was

administered until preoperative activated clotting time was achieved. The operation field was inspected for bleeding and drains, pacing wires were inserted, and the median sternotomy was closed.

### Sonolysis and Sham Procedure

Sonolysis was undertaken as continuous Doppler monitoring of the right MCA from the start of intervention (CABG or valve surgery) using a diagnostic transcranial Doppler system (MultiDop T1; DWL Elektronische Systeme GmbH, Sipplingen, Germany) and a 2-MHz diagnostic transcranial Doppler probe. The probe was fixed in the required position using a helmet with an insonation depth of 55 mm, sample volume of 10 mm, power of 200 mW, and a thermal index for cranial bone (TIC) of 3.1. The device sound and Doppler wave imaging were disabled to maintain blinding of the intervention team. Hence, no subjects were monitored for changes in blood flow or microemboli during the intervention/sham period. Patients in the control group underwent a sham procedure in which the helmet was fixed, blood flow from the MCA detected, but further sonolysis (transcranial Doppler monitoring) was not conducted.

### MRI

MRI was acquired using a 1.5-T Avanto system (Siemens, Erlangen, Germany). The protocol comprised 4 sequences. The first sequence was a transverse T2-weighted spin echo. The second sequence was a fluid-attenuated inversion recovery (FLAIR). The third sequence was a diffusion-weighted imaging (DWI) with apparent diffusion coefficient maps (b, representing a factor of diffusion-weighted sequences  $b = 0$  and  $b = 1000$  s/mm<sup>2</sup>; echo time, 130 ms; repetition time, 4500 ms; section thickness, 5.0 mm; gap, 1 mm; matrix size, 192 × 192; number of excitations, 4; FOV, 255 mm; FOV ph, 100%; bandwidth, 1240 Hz/Px; echo spacing, 0.93 ms). The final sequence was a T2 star-weighted gradient-recalled echo. This sequence was performed for detection of bleeding including microbleeds. For MRI, we used the same protocol as in our previous study.<sup>23</sup>

Sequences were applied at an identical level with the same slice thickness and identical cut number. Slice thickness comprised the cut thickness (5 mm) + gap (10%). The standard number of slices was 25. The standard slice level was considered to be a modified level of the skull base owing to minimalization of the distant-artifacts echo planar imaging sequence.

In accordance with previous studies,<sup>24–26</sup> new ischemic brain lesions were defined as “hyperintense regions” on post-intervention DWIs that were not present on pretreatment images. The location, number, and volume of hyperintense lesions on DWI were evaluated by a radiologist and neurologist blinded to the treatment allocation, with disagreements resolved by consensus. Volume was calculated as the total hyperintense area in each single slice multiplied by the effective slice thickness. Ischemic lesions <0.5 mL or ≥0.5 mL were evaluated separately in the subanalyses. New ischemic lesions in the brain were classified as “ipsilateral” or “contralateral” to the treated vessel. Enlargement of a previous DWI lesion was not considered a new ischemic lesion.

### Clinical Examinations

Age, sex, comorbidities (arterial hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, angina pectoris, heart failure, atrial fibrillation, history of myocardial

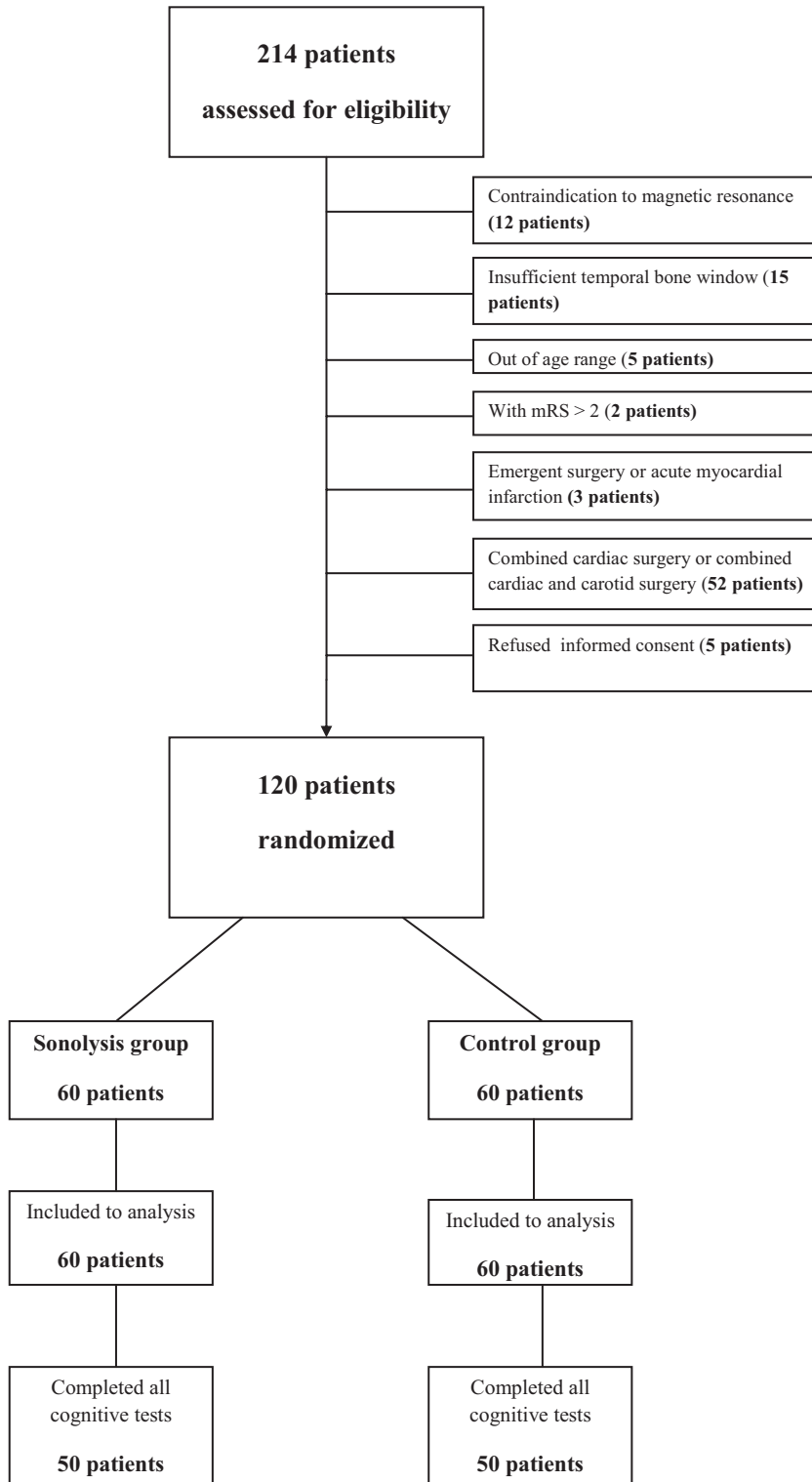


FIGURE 1. Flow chart diagram of the study. mRS = modified Rankin score.

infarction, history of transient ischemic attack [TIA] or stroke, peripheral arterial disease, hyperlipidemia, atrial fibrillation), current medications (antiplatelet drugs [eg, acetylsalicylic acid, clopidogrel], anticoagulants, antihypertensives, oral antidiabetics), insulin and hypolipidemic agents [including statin dose]), smoking status, alcohol use, internal carotid artery (ICA) stenosis  $\geq 50\%$ , and type of intervention were documented. Physical and neurologic examinations evaluating neurologic deficits, dependency (assessed using a modified Rankin scale), and cognitive function were conducted before, 24 h after, and 30 days after cardiac surgery by a neurologist blinded to treatment groups. Cognitive function was tested using the Addenbrooke Cognitive Examination Revised (ACE-R), Mini Mental State Examination (MMSE), clock-drawing test, and verbal fluency test.

### Endpoints for Study Analyses

Primary endpoints were the prevalence and volume of new brain ischemic lesions and new brain ischemic lesions  $>0.5$  mL in the right MCA territory on control brain DW-MRI 24 to 72 hours after intervention in sonolysis and control groups. Secondary endpoints were the prevalence of stroke or TIA within 30 days and changes in cognitive function as evidenced by scores for ACE-R, MMSE, clock-drawing test, or verbal

fluency test 30 days postprocedure relative to pretreatment scores.

### Statistical Analyses

Sample size was based on an expected 20% reduction of new ischemic lesions on DW-MRI in the sonolysis group (estimated prevalence, 10%) compared with the control group (estimated prevalence, 30%). Prestudy calculations using  $\chi^2$  test with a continuity correction showed that  $\geq 60$  patients in each group were needed to reach a significant difference with an  $\alpha$  value of 0.05 (2-tailed) and a beta value of 0.8.

Data were analyzed using SPSS v22.0 (IBM, Armonk, NY). Normality of data distribution was checked using the Shapiro-Wilk test. Data with a normal distribution (age, delay between symptoms and intervention) are reported as mean  $\pm$  standard deviation. Remaining variables are presented as the mean, median, and interquartile range. Categorical variables in the 2 arms were compared by Fisher exact test. Continuous variables were compared by the Mann-Whitney *U* test. The following variables were included in univariate and multiple logistic regression analyses: age; sex; arterial hypertension; diabetes mellitus; coronary heart disease; angina pectoris; heart failure; atrial fibrillation; history of myocardial infarction; history of TIA or stroke; peripheral arterial disease;

**TABLE 1.** Patients Demographic Data

	Sonolysis Group	Control Group	P
Number of patients	60	60	NA
Age, y; mean, median (IQR)	65.3, 66.5 (61–71)	66.8, 69.0 (64–73)	0.280
Male, n (%)	37 (61.7)	32 (53.3)	0.460
CABG, n (%)	31 (51.7)	29 (48.3)	0.855
Valve surgery, n (%)	29 (48.3)	31 (51.7)	0.855
ICA stenosis $\geq 50\%$ , n (%)	6 (10.0)	4 (6.7)	0.743
Arterial hypertension, n (%)	48 (80.0)	47 (78.3)	1.000
Diabetes mellitus, n (%)	23 (38.3)	19 (31.7)	0.566
Hypelipidemia, n (%)	33 (55.0)	38 (63.3)	0.458
Ischemic heart disease, n (%)	42 (70.0)	40 (66.7)	0.845
Angina pectoris, n (%)	24 (40.0)	23 (38.3)	1.000
History of myocardial infarction, n (%)	14 (23.3)	12 (20.0)	0.825
Heart failure, n (%)	5 (8.3)	5 (8.3)	1.000
Atrial fibrillation, n (%)	33 (55.0)	30 (50.0)	0.715
History of stroke or TIA, n (%)	3 (5.0)	3 (5.0)	1.000
Peripheral arterial disease, n (%)	3 (5.0)	3 (5.0)	1.000
Smoking, n (%)	6 (10.0)	6 (10.0)	1.000
Alcohol abuse, n (%)	1 (1.7)	0 (0.0)	1.000
Statin use, n (%)	37 (61.7)	41 (68.3)	0.566
Statin dose, mg, mean, median (IQR)	26.2, 40 (0–40)	29.0, 40 (0–40)	0.429
Oral antidiabetics, n (%)	11 (18.3)	12 (20.0)	1.000
Insulin, n (%)	10 (16.7)	6 (10.0)	0.421
Antihypertensives, n (%)	56 (93.3)	57 (95.0)	1.000
Antiplatelets, n (%)	26 (43.3)	24 (40.0)	0.853
Anticoagulation, n (%)	34 (56.7)	36 (60.0)	0.853
ACE-R, points, mean, median (IQR)	79.9, 80 (74–85)	80.2, 81.5 (75–86)	0.441
MMSE, points, mean, median (IQR)	27.5, 28, (26–29)	26.9, 27, (25–29)	0.185
Clock test, points, mean, median (IQR)	4.1, 4, (4–5)	4.1, 4, (4–5)	0.653
Verbal fluency test, points, mean, median (IQR)	3.6, 3, (2–5)	3.3, 3, (2–4)	0.294

ACE-R = Addenbrooke's Cognitive Examination Revised, CABG = carotid artery bypass graft, ICA = internal carotid artery, IQR = interquartile range, MMSE = Mini Mental State Examination, NA = not applicable, SD = standard deviation, TIA = transient ischemic attack.

**TABLE 2.** Study Results

	Sonolysis Group	Control Group	P
New brain ischemic lesion in the right MCA territory, n (%)	8 (13.3)	16 (26.7)	0.109
Volume of ischemic lesion in the right MCA territory, mL, mean, median (IQR)	0.0, 0.0 (0.0–0.0)	0.7; 0.0 (0.0–0.1)	0.026
New brain ischemic lesions ≥0.5 mL in the right MCA territory, n (%)	1 (1.7)	9 (15.0)	0.017
New brain ischemic lesion, n (%)	18 (30.0)	23 (38.3)	0.442
Volume of ischemic lesion, mL, mean, median (IQR)	0.0, 0.0 (0.0–0.1)	0.7; 0.0 (0.0–0.2)	0.182
New brain ischemic lesions ≥0.5 mL in the right MCA territory, n (%)	4 (6.7)	13 (21.7)	0.034
Stroke or TIA within 30 days, n (%)	0 (0.0)	2 (3.3)	0.496
Serious adverse event, n (%)	42 (70.0)	44 (73.3)	0.840
Death within 30 days, n (%)	3 (5.0)	1 (1.7)	0.619

IQR = interquartile range, MCA = middle cerebral artery, TIA = transient ischemic attack.

hyperlipidemia; use of antihypertensives, oral antidiabetics, insulin, antiplatelets, anticoagulants, statins, including statin dose (simvastatin equivalent dose); smoking; alcohol abuse; ICA stenosis ≥50%; type of intervention. All tests were carried out at an α level of significance of 0.05.

**RESULTS**

In total, 120 of 214 screened patients fulfilled the inclusion criteria (Figure 1). Subjects were allocated to the sonolysis or control group randomly and equally. Clinical and procedural variables between the groups were well balanced (Table 1). No patient was lost to follow-up. Twenty subjects refused to complete cognitive tests on particular visits.

New ischemic lesions in the right MCA territory on DW–MRI were found in 8 cases in the sonolysis group and 16 patients in the control group (13.3 vs 26.7%, *P* = 0.109). The sonolysis group exhibited a significantly reduced median volume of new brain ischemic lesions (*P* = 0.026) and a proportion of larger (≥0.5 mL) new brain ischemic lesions (*P* = 0.017) in the right MCA territory (Table 2). Significant reductions in the total number of larger (≥0.5 mL) brain ischemic lesions (*P* = 0.034) were detected in the sonolysis group (Table 2). Stroke or TIA did not occur in any of the patients in the sonolysis group, but did occur in 2 cases in the control group (*P* = 0.496). Three deaths were recorded in the sonolysis group and 1 in the control group (*P* = 0.619) (Table 2). There was no significant correlation between statin

dose and volume of the brain ischemic lesion (*r* = 0.07, *P* = 0.442).

Stepwise multiple logistic regression analyses revealed only ICA stenosis ≥50% and smoking as independent predictors of larger (≥0.5 mL) brain ischemic lesion, with odds ratios (ORs) of 5.685 (95% confidence interval [CI], 1.272–25.409, *P* = 0.023) and 4.698 (95% CI, 1.092–20.208, *P* = 0.038), respectively.

There were no significant differences in cognitive-test scores 30 days after intervention between sonolysis and control groups (Table 3). Regardless of the group, patients with new ischemic lesions showed significant worsening in MMSE after intervention (*P* = 0.048) in comparison with patients without a new ischemic lesion. However, no significant differences were found for other cognitive tests (*P* > 0.05 in all cases) (Table 4).

**DISCUSSION**

Three recent meta-analyses concluded that sonolysis is a promising treatment for patients who have suffered acute ischemic stroke.<sup>9,27,28</sup> Furthermore, the Sonolysis in Prevention of Brain Infarctions during Carotid Stenting and Carotid Endarterectomy (SONOBUSTER) trial demonstrated the effect of intraoperative sonolysis in reduction of the prevalence and volume of new brain ischemic lesions after carotid endarterectomy and carotid stenting.<sup>29</sup> Results of the present study also support the safety and efficacy of sonolysis for prevention of periprocedural brain ischemic lesions in patients undergoing

**TABLE 3.** Results of Cognitive Tests

	Sonolysis Group, Mean, Median, (IQR)	Control Group, Mean, Median, (IQR)	P
ACE-R – after 30 days, points	80.2, 80 (74 to 85)	80.6, 82 (76 to 87)	0.344
– change from baseline, points	0.3, 0 (–1 to 2)	0.4, 0 (–1 to 2)	0.670
MMSE – after 30 days, points	27.7, 28 (26 to 29)	27.0, 28 (26 to 29)	0.208
– change from baseline, points	0.2, 0 (0 to 1)	0.1, 0 (0 to 0)	0.860
Clock drawing test – after 30 days, points	4.5, 5 (4 to 5)	4.3, 5 (4 to 5)	0.491
– change from baseline; points	0.4, 0 (0 to 0)	0.2, 0 (0 to 0)	0.276
Verbal fluency test – after 30 days, points	3.6, 3 (2 to 5)	3.4, 3 (2 to 5)	0.726
– change from baseline, points	0.0, 0 (0 to 0)	0.1, 0 (0 to 1)	0.529

ACE-R = Addenbrooke Cognitive Examination Revised, IQR = interquartile range, MMSE = Mini Mental State Examination.

**TABLE 4.** Results of Cognitive Tests in Patients With and Without New Brain Ischemic Lesion on Control Magnetic Resonance

	Patients Without a New Brain Ischemic Lesion, Mean, Median (IQR)	Patients With a New Brain Ischemic Lesion, Mean, Median (IQR)	P
ACE-R – after 30 days, points	80.7, 80 (75 to 85)	80.2, 82 (74 to 87)	0.464
– change from baseline, points	0.3, 0 (–1 to 2)	0.6, 0.5 (–0.25 to 1.25)	0.187
MMS – after 30 days, points	27.5, 28 (26 to 29)	26.6, 27.5 (25 to 28)	0.046
– change from baseline, points	0.3, 0 (0 to 0)	–0.3, 0 (–1 to 0)	0.048
Clock drawing test – after 30 days, points	4.5, 5 (4 to 5)	4.3, 5 (4 to 5)	0.312
– change from baseline, points	0.3, 0 (0 to 0)	0.3, 0 (0 to 0.25)	0.401
Verbal fluency test – after 30 days, points	3.6, 3 (2 to 5)	3.2, 3 (2 to 4.5)	0.227
– change from baseline, points	0.0, 0 (0 to 0)	0.1, 0 (0 to 0)	0.288

ACE-R = Addenbrooke Cognitive Examination Revised, IQR = interquartile range, MMSE = Mini Mental State Examination.

CABG or valve surgery. The sonolysis groups exhibited a significant reduction in the prevalence of larger new ischemic lesions and lesion volume in the brain after cardiac surgery. Unlike studies using sonolysis in acute stroke patients, not a direct effect of ultrasound waves on the clot but mainly an activation of fibrinolytic system was used in the SONOBUSTER Trial and in the presented SONORESCUE Trial.<sup>29,30</sup>

Published studies have demonstrated the effect of sonolysis on acceleration of arterial recanalization when combined with intravenous thrombolysis in patients with acute stroke.<sup>9,15,16</sup> Moreover, recent studies have also shown the effect of sonolysis on activation of endogenous fibrinolytic enzymes in healthy volunteers<sup>30</sup> and acute-stroke patients without application of thrombolytic agents.<sup>9,17,18</sup> The mechanisms responsible for a reduced prevalence and volume of lesions after sonolysis in the present study could include acceleration of enzymatic fibrinolysis by the direct activation of a fibrinolytic system and increased transport of fibrinolytic agents (eg, plasmin) into the thrombus by mechanical disruption of thrombus structure, destruction of gaseous bubbles, and transient peripheral vasodilatation.<sup>9,20</sup>

DW-MRI is sufficiently sensitive for detection of small ischemic lesions in the brain after CABG or valve surgery.<sup>24–26</sup> Conversely, relatively few TIAs or strokes are expected after these types of cardiac surgery ( $\approx 3\%$ )<sup>1–3</sup>, similar to the levels seen in patients undergoing carotid endarterectomy or stenting.<sup>31,32</sup> Thus, DW-MRI is being used increasingly as a surrogate marker for stroke.<sup>24–26</sup> In addition to imaging manifestations of brain ischemia, cognitive changes represent important signs of ischemic lesions in the brain after cardiac surgery. Studies have suggested that perioperative brain injury caused by embolization of the neurovasculature during cardiac surgery is associated with temporary postoperative cognitive dysfunction and may trigger chronic or progressive dementia.<sup>8</sup> We found no differences in cognitive function between sonolysis and control groups, but patients with a new brain ischemic lesion on control MRI showed significant worsening in MMSE. However, the study cohort was too small to reach significance for changes in cognitive function.

Smoking (OR = 4.6) and ICA stenosis  $\geq 50\%$  (OR = 5.7) were identified as the only independent predictors of larger brain ischemic lesion. Results of the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) Trial identified smoking is an independent predictor of the composite endpoint of death, myocardial

infarction, and stroke with hazard ratio of 1.8.<sup>33</sup> Atherosclerosis in cervical and cerebral arteries is the other important etiopathogenetic factor of stroke in patients undergoing cardiac surgery.<sup>34</sup> Studies have identified carotid-artery stenosis as a risk factor for perioperative stroke.<sup>35–39</sup> Anticoagulation, turbulent blood flow, and hypertension during CABG could be responsible for an increased intraoperative risk of intraplaque hemorrhage and subsequent distal embolization.<sup>34</sup> Impaired cerebral hemodynamic function distal to carotid-artery stenosis is another determinant of postoperative stroke.<sup>40,41</sup>

### Study Limitations

The limited number of randomized patients did not allow comparison of the perioperative risk of stroke/TIA, mortality, or cognitive dysfunction among groups. Serial follow-up FLAIR and DW-MRI were not conducted to compare the progression/persistence of ischemic lesions. Moreover, ischemic lesion volume was estimated by manual means.

### CONCLUSIONS

Intraoperative sonolysis can reduce the prevalence of larger ( $\geq 0.5$  mL) ischemic lesions and the volume of new ischemic lesions in the brain after cardiac surgery. ICA stenosis  $> 50\%$  and smoking are independent predictors for larger ( $\geq 0.5$  mL) ischemic lesions in the brain.

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