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Heparin and Air Filters Reduce Embolic Events Caused by Intra-Arterial Cerebral Angiography

A Prospective, Randomized Trial

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Background—Intra-arterial cerebral angiography is associated with a low risk for neurological complications, but clinically silent ischemic events after angiography have been seen in a substantial number of patients.

Methods and Results—In a prospective study, diffusion-weighted magnetic resonance imaging (DW-MRI) before and after intra-arterial cerebral angiography and transcranial Doppler sonography during angiography were used to evaluate the frequency of cerebral embolism. One hundred fifty diagnostic cerebral angiographies were randomized into 50 procedures, each using conventional angiographic technique, or systemic heparin treatment throughout the procedure, or air filters between the catheter and both the contrast medium syringe and the catheter flushing. There was no neurological complication during or after angiography. Overall, DW-MRI revealed 26 new ischemic lesions in 17 patients (11%). In the control group, 11 patients showed a total of 18 lesions. In the heparin group, 3 patients showed a total of 4 lesions. In the air filter group, 3 patients exhibited a total of 4 lesions. The reduced incidence of ischemic events in the heparin and air filter groups compared with the control group was significantly different ($P=0.002$). Transcranial Doppler sonography demonstrated a large number of microembolic signals that was significantly lower in the air filter group compared with the heparin and control groups ($P<0.01$), which did not differ from each other.

Conclusions—Air filters and heparin both reduce the incidence of silent ischemic events detected by DW-MRI after intra-arterial cerebral angiography and can potentially lower clinically overt ischemic complications. This may apply to any intra-arterial angiographic procedure. (*Circulation*. 2004;110:2110-2115.)

Key Words: angiography ■ ischemia ■ magnetic resonance imaging ■ complications ■ embolism

Intra-arterial digital subtraction angiography (IA-DSA) has remained the “gold standard” in the assessment of cerebral vessels. In such disorders as vasculitis or intracranial aneurysms, the sensitivity and specificity of such noninvasive techniques as CT angiography and MR angiography do not suffice to replace intra-arterial angiography.¹ IA-DSA harbors a substantial risk for procedure-related symptomatic cerebral ischemia (1% to 3% in previous studies²⁻⁵). We have recently shown that clinically silent ischemic events identified by diffusion-weighted MRI (DW-MRI) can be found in as many as 23% of patients undergoing IA-DSA.⁶ This has been confirmed by other investigators.^{7,8} Moreover, silent cerebral embolism has also been shown in extracranial angiographic procedures.⁹ Basically, embolic events during IA-DSA may be caused by either thromboembolism or air embolism introduced by injection of contrast medium or catheter flushing.

A high number of microembolic signals (MESs) have been identified by transcranial Doppler sonography during cerebral angiography.¹⁰ The clinical relevance of this finding, however, is uncertain, because no correlation between microembolism and morphological brain damage or clinical symptoms has been reported.

In the present study, we investigated the effect of air filters and heparin during IA-DSA on the incidence rate of ischemic lesions as identified by DW-MRI and of MESs assessed by transcranial Doppler sonography. These findings were compared with those of a control group subjected to conventional IA-DSA.

Methods

Patients and Protocol

From March 2000 to June 2002, all patients scheduled for IA-DSA were assessed for eligibility in the study. Patient characteristics are

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TABLE 1. Patient Characteristics of the 3 Groups Under Study

	Heparin	Air Filter	Control
Age, mean±SD, y	49.3±13.5 (55±8.7)	49.4±13 (60.3±8.1)	51.5±14.2 (55±11.3)
Female/male	30/20 (2/1)	25/25 (3/0)	26/24 (6/5)
Vascular risk factors	16 (1)	16 (3)	17 (8)
Preexisting lacunae on MRI	5 (1)	6 (1)	9 (3)
Vascular encephalopathy (DWMH and PVH) on MRI ²	8 (1)	11 (3)	14 (7)
Mean fluoroscopy time, min±SD	13.2±15.7 (16.1±3.8)	11.3±11 (34.3±14)	13.2±15.7 (21.6±27.7)
Mean contrast medium, mL±SD	108.6±53.1 (183.3±57.7)	116.6±50.6 (240±52.9)	112.6±46.1 (111.8±44.3)

DWMH indicates deep and subcortical white matter hyperintensities. Values in parentheses represent patients with ischemic lesions on DW-MRI.

summarized in Table 1. Exclusion criteria were recent hemorrhage, any preexisting anticoagulation, need for interventional angiographic procedures, necessity of a power injector for the aortic arch, age <18 years, emergency angiography, or no consent to participate in the study. Patients were randomized shortly before the procedure to one of the 3 groups (conventional technique, heparin, or air filter) by means of closed envelopes containing the group allocation that were opened by a person not involved in the study. The study was approved by the Ethics Committee of the University of Würzburg, and written informed consent was obtained from every patient 24 hours before the examination.

Patients underwent a neurological examination before, immediately after, and 1 day after IA-DSA. A neurological complication was defined as any new cranial nerve, motor or sensory deficit, reflex change, pyramidal sign, or mental alteration during angiography or within the 24-hour follow-up period. All patients were assessed for cerebrovascular risk factors, which were defined as previous stroke or transient ischemic attack, hypertension, diabetes, and carotid artery stenosis. MRI was applied before and within 3 days (median, 1 day) after angiography on a 1.5-T unit (Magnetom Vision or Magnetom Symphony, Siemens). The MRI protocol included a T2-weighted double spin echo sequence (TR 2000 ms, TE 20/80 ms) and a diffusion-weighted sequence (EPI, 3 orthogonal-axis diffusion-weighted images, TR=5400 ms, TE=103 ms, b=0, 500 and 1000 s/mm²). Blinded to clinical examination and group assignment, 2 neuroradiologists (M.B. and L.S.) independently analyzed the images with respect to diffusion abnormalities on DW-MRI and preexisting cerebral vascular encephalopathy on T2-weighted images according to the criteria of Fazekas et al.¹¹ This classification defines and grades vasculopathy as deep and subcortical white matter hyperintensities, periventricular hyperintensities, and lacunae.

Continuous transcranial Doppler examination (Neuroguard, EME Nicolet) of the right and left middle cerebral arteries was performed through the temporal bone windows starting 5 minutes before the catheterization until the end of the procedure, applying an embolus detection software (Embotec, Stac GmbH). The investigation was run with two 2-MHz probes fixed to the patient's head. The depth of insonation was between 48 and 55 mm. All data were stored on digital audio tapes (DAT) for offline analysis, and the evaluation was performed with the observer blinded with regard to the patient data. According to Markus et al.¹⁰ 2 patterns of MESs were identified (Figure 1): First, we observed single MESs, which were seen during any phase of IA-DSA, mostly with vessel probing or flushing of the catheter (Figure 1A). These were identified according to published criteria¹² and counted manually. Second, we identified dense showers of MESs, which were observed during injection of contrast medium (Figure 1B). Because it was impossible to resolve single MESs in this pattern, the overall time of the MES shower was determined in seconds, as described previously.¹⁰

Procedures

In all patients, an established angiographic technique⁶ was applied, including the following criteria: transfemoral approach, high-pressure (300 mm Hg) continuous catheter flushing with saline unless a guidewire was used, a 4F or 5F standard catheter (4F

Vertebral or Head Hunter, Terumo), a standard guidewire (Radifocus, Ø=0.035 in, Terumo) and nonionic contrast medium (Imeron 250, Bracco-Byk Gulden) injected manually using a 10-mL plastic angiographic syringe. All IA-DSAs were performed by one of 5 experienced board-certified neuroradiologists. The medical indications for angiography are shown in Table 2. In patients receiving heparin, an intravenous bolus of 50 IU/kg BW (Liquemin, Hoffmann La Roche AG) was applied over a period of 15 minutes after placement of the transfemoral sheath and before beginning IA-DSA, followed by a maintenance dose of 25 IU · kg BW⁻¹ · h⁻¹ throughout the procedure. Heparin was not reversed at the end of the procedure. In the air filter group, filters (Intrapur, Braun; filter pore size, 1.2 µm) were placed between the catheter and both the catheter flushing and the syringe containing the contrast medium. In the control group, a technique identical to that used in group A or B was used except for heparin or air filters. For every patient, total fluoroscopy time, amount of contrast medium, and the number of catheters used were recorded. At the end of the procedure, manual compression of the puncture site was performed for 15 minutes, followed by strict bed rest and a tight compression bandage for 24 hours.

Statistical Analysis

For statistical analyses, the R environment for statistical computing (R 1.8.1, <http://www.r-project.org/>; sm library version 2) was used. Pearson's χ^2 test was performed on tabulated contingencies of the incidence of new lesions on DW-MRI and preexisting vascular encephalopathy on MRI. Because the continuous and ordinal data were not normally distributed ($P \leq 0.001$, Shapiro-Wilk normality test), nonparametric tests were applied as indicated.

The sample size calculation was based on previous data revealing a total of 32 new ischemic lesions in 66 diagnostic angiographies.⁶ Assuming a reduction in the number of lesions by 50%, a minimum of 50 patients per group would be required to reject the null hypothesis at a significance level of $P=0.05$ difference with a power of 0.8.

Results

Of the 1499 patients seen in the study period, 178 met the inclusion criteria (Figure 2). Twenty-eight patients had to be excluded after randomization because of withdrawal of consent ($n=5$) or for lack of MRI after angiography ($n=23$). The 3 patient groups entering the trial were homogeneous with respect to age, sex, and history of vasculopathy and were balanced as to the presence of lacunae ($P=0.552$, H-ANOVA) or diffuse vascular encephalopathy on MRI¹¹ ($P=0.227$, H-ANOVA; Table 1). Neither fluoroscopy time ($P=0.554$, H-ANOVA) nor the amount of contrast medium given ($P=0.408$, H-ANOVA) differed between the study groups (Table 1).

There was no new neurological deficit after any IA-DSA. Before angiography, there were no lesions on DW-MRI. After angiography, 17 patients (11%) revealed a total of 26

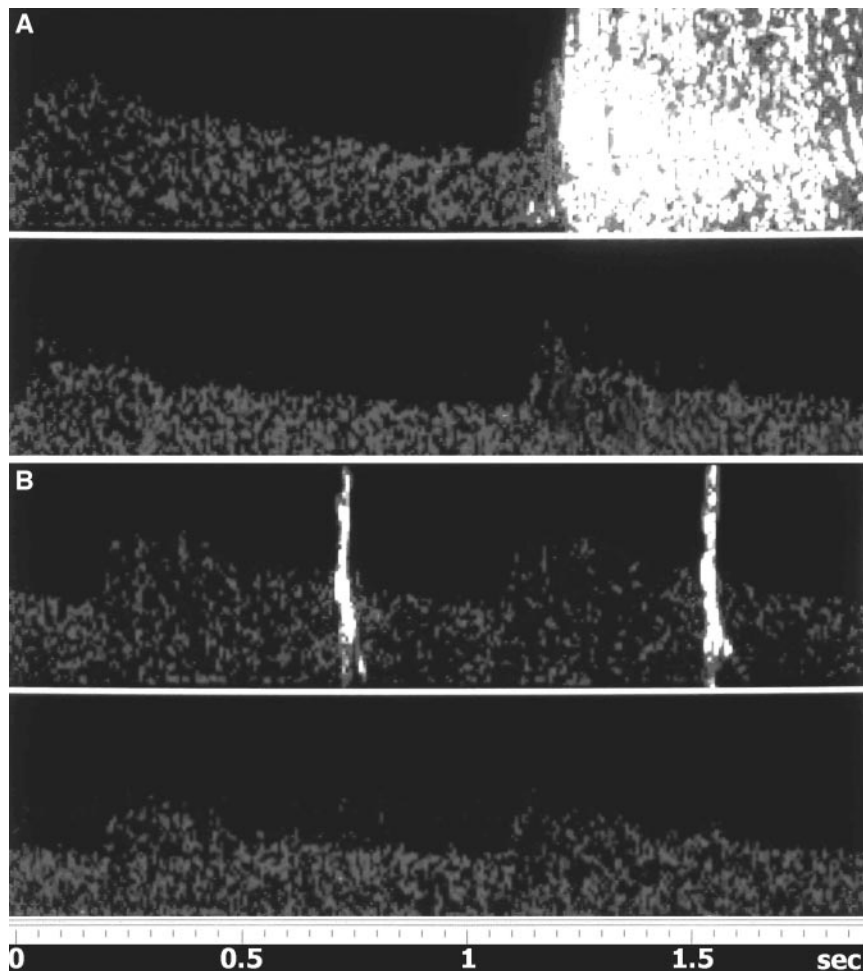


Figure 1. MESs during intra-arterial cerebral angiography. Transcranial Doppler sonography of both middle cerebral arteries during angiography using a conventional IA-DSA technique. A, A dense shower of MESs is depicted during injection of contrast medium. Single MESs are not discernible. B, Single MESs are shown in same patient during probing of common carotid artery. Time scale applies to A and B.

new ischemic lesions. All lesions were suggestive of an embolic pattern (ie, cortical or subcortical location and/or in the vascular territory of perforating arteries, Figure 3). In the control group, 11 patients (22%) developed 17 lesions. In the heparin group, 3 patients (6%) revealed 4 new lesions. Similarly, in the air filter group, 3 patients (6%) exhibited 4 new lesions (Table 2). Thus, the total lesion count was lower in the 2 treatment groups than the control group ($P=0.002$, χ^2). Moreover, the number of patients revealing a new lesion was lower in both the heparin and air filter groups than the control group ($P=0.044$, χ^2). There was no interobserver disagreement in the detection of ischemic lesions.

Patients with ischemic lesions more frequently had a history of vasculopathy than patients without postangio-

graphic lesions ($P<0.001$, χ^2), and they more often revealed a diffuse white matter hyperintensity ($P<0.001$, χ^2) and periventricular hyperintensities ($P<0.001$, χ^2) on MRI (Table 1). Patients with preexisting vasculopathy ($n=49$) required longer fluoroscopy times and more contrast medium than those without vascular risk factors ($P<0.001$, U test).

Furthermore, the postangiographic frequency of ischemic lesions correlated positively with the angiographic fluoroscopy time (Kendall's $\tau=0.18$, $z=3.24$, $P<0.001$). This association was reduced by treatment with either heparin or air filters (nonparametric ANCOVA testing for equality, $P=0.009$, and parallelism, $P=0.793$). However, the longer the fluoroscopy time, the more the initial benefit of air filters seemed to vanish compared with the group treated with heparin (nonparametric ANCOVA testing for equality, $P=0.014$, and parallelism, $P=0.002$). These findings are illustrated by the nonparametric logistic regression plots of fluoroscopy time versus the probability to develop 1 or more ischemic lesions (Figure 4): both air filters and heparin reduced the probability to acquire an ischemic lesion compared with the control group. This effect, however, was dependent on the fluoroscopy time: At short fluoroscopy times, the protective effect of the air filter appeared more clearly, whereas at longer fluoroscopy times, this effect diminished and then disappeared, whereas the protective effects of heparin became more apparent. Even in the heparin

TABLE 2. Medical Indication for IA-DSA

Medical Indication	Heparin	Air Filter	Control
Tumor	7 (1)	4	6
Arteriovenous fistula	8 (1)	9 (1)	6 (4)
Aneurysm	13	18 (1)	22 (4)
Extracranial/intracranial stenosis	4 (1)	3	4 (2)
Arteriovenous malformation	11	8	7
Vasculitis	3	4 (1)	4 (1)
Other	4	4	1

Values in parentheses represent patients with ischemic lesions on DW-MRI.

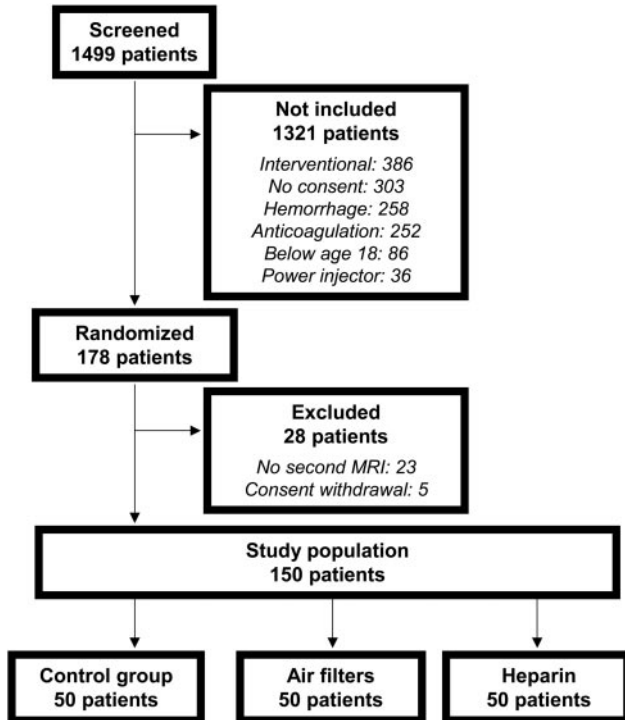


Figure 2. Trial flow chart.

group, the incidence of ischemic lesions increased with longer fluoroscopy times, but to a lesser degree than in the control and air filter groups (Figure 4).

Catheter exchanges were not performed more frequently in patients with new lesions on DW-MR (3 catheter exchanges in 17 patients with lesions versus 5 catheter exchanges in 133 patients without lesions, $P=0.07$, Fisher's exact test). Moreover, the total number of catheters used was not increased in the group of patients with ischemic lesions (21 catheters in 17 patients versus 141 catheters in 133 patients, $P=0.79$, χ^2).

The results of MES detection are shown in Table 3. In six patients, transcranial Doppler sonography was technically not feasible because of an inaccessible bone window (2 in the heparin group, 1 in the air filter group, 3 in the control group). The median number of single MESs was lower in the air filter group than in the heparin group ($P=0.006$, U test) and in the control group ($P<0.001$, U test). There was no difference between the heparin and the control groups ($P=0.179$, U test). The overall duration of MES showers was significantly reduced in the air filter group compared with the heparin group ($P<0.001$, U test) and with the control group ($P<0.001$, U test), which did not differ from each other ($P=0.280$, U test). Dense showers of MESs were observed exclusively during injection of contrast medium. The beginning and end of these MES showers was slightly delayed in relation to the contrast injection. Single MESs, however, were not related to any specific angiographic procedure but rather were observed during all phases of angiography. Patients revealing a new ischemic lesion on DW-MRI had more single MES events ($P=0.041$, U test), whereas the duration of MES showers did not differ ($P=0.201$, U test). There were no groin hematomas in the present series of 150 patients.

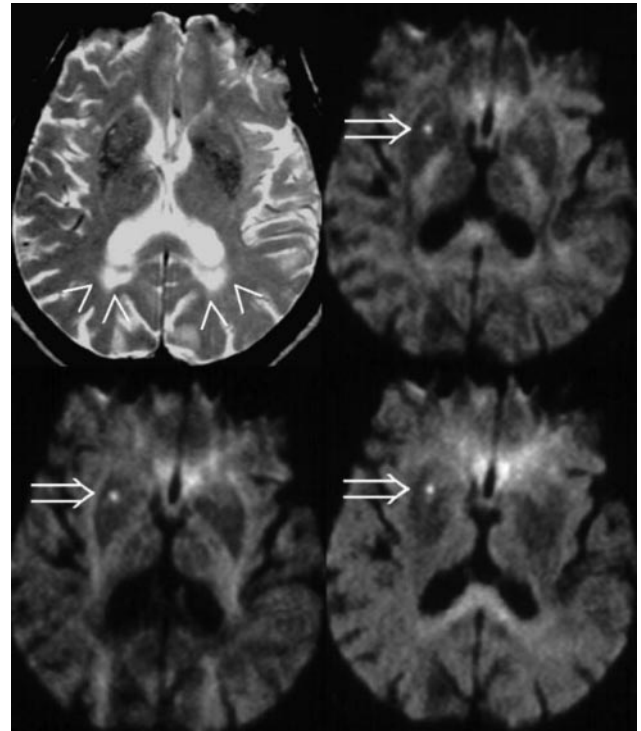


Figure 3. Ischemic lesions on postangiographic MRI: axial T2-weighted (top left) and orthogonal axis diffusion-weighted images at same level. MR images of a 66-year-old patient undergoing intra-arterial angiography for suspected vasculitis. On T2-weighted images, there is marked hyperintensity of white matter, indicating preexisting vasculopathy (arrowheads). On DW-MRI, a new, presumably embolic ischemic lesion is present in right lentiform nucleus (arrow).

Discussion

Over recent years, minimally invasive endovascular procedures have become increasingly important. Nevertheless, all intra-arterial procedures harbor a certain risk for procedure-related vessel occlusion, with the risk for subsequent tissue infarction. DW-MRI is a novel specific and sensitive MR technique for detection of acute cerebral ischemia.¹³ Recently, DW-MRI was introduced as a surrogate marker for subclinical ischemic brain damage not only after IA-DSA⁶⁻⁸ but also after extracranial angiographic procedures⁹ and such nonangiographic interventions as cardiac surgery.¹⁴ As the principal finding of this study, we show an independent reduction of ischemic lesions from 22% in a control group undergoing IA-DSA to 6% by treatment with either heparin or air filters. This finding underscores the relevance of both thromboembolism and air embolism to the overall ischemic complications after intra-arterial angiography.

Symptomatic air embolism¹⁵ and thromboembolism¹⁶ are recognized complications known to occur after various angiographic procedures, including coronary angiography. However, little is known about the frequency of procedure-related subclinical ischemic tissue damage. An asymptomatic elevation of cardiac enzymes has been described in a substantial number of patients undergoing endovascular cardiac interventions.¹⁷ Because postangiographic lesions on DW-MRI represent structural tissue damage,^{6,7} our findings may

be considered a surrogate model and may have implications not only for cerebral angiography but also for any other intra-arterial procedure with an intrinsic risk of embolic complications.

In experimental studies, heparin treatment has been demonstrated to substantially lower the overall thromboembolic complication in diagnostic and interventional cardiac procedures.¹⁸ The risk for embolism in the present study and in our previous report⁶ was strongly associated with a history of vasculopathy and with technical aspects such as fluoroscopy time and difficulties in probing the appropriate arteries. Our findings indicate that the longer the angiographic procedure lasts, the better these procedure-related ischemic events may be prevented by systemic heparin treatment rather than by the use of air filters alone. Longer and more difficult angiographic procedures seem to enhance the risk of thromboembolism more than the risk of air embolism, whereas the risk of air embolism may prevail over the risk of thromboembolism during short and less difficult procedures. This may be explained by the elimination of air bubbles from the catheter and flushing system at the very beginning of the angiographic procedure.

A potential disadvantage of using heparin during angiography is an increased rate of groin hematomas, which were not seen in this study population, probably because of strict immobilization and local compression. In the study by Dion et al,² patients received a bolus of 2000 IU heparin. Hematomas at the puncture site were reported in 6.9% of those patients. In a recent study by Willinsky et al,⁵ heparin was rarely used (1.7% of patients). In this series, groin hematomas were observed in only 0.4% of all patients. However, a low rate of hematomas (1.1%) has also been reported in a large study of patients with a 7F or 8F femoral sheath receiving a bolus of 5000 IU of heparin during angiography.¹⁹ In case of bleeding or hematomas at the puncture site, heparin can quickly be reversed with protamine.

In the literature, most case reports on symptomatic air embolism are described during cerebral^{20,21} and coronary angiography.^{15,22} Numerous small air emboli have been demonstrated during catheter flushing²³ and contrast medium injections.⁹ However, little is known about the actual risk of air embolism. Here, we demonstrate a marked reduction of ischemic lesions on DW-MRI by using air filters between the catheter and both the catheter flushing and the contrast medium syringe. This finding suggests that a substantial number of silent ischemic lesions after angiography may indeed be caused by air embolism and can be prevented by appropriate filters.

In the absence of neurological symptoms, the clinical relevance of bright lesions on DW-MRI needs to be critically discussed. These silent lesions obviously represent morphological brain damage⁶ and, if located in an eloquent brain area such as the internal capsule or the precentral gyrus, contralateral hemiparesis may be caused despite a small lesion size.²⁴ It can be anticipated that in a cohort of patients larger than the present study groups, symptomatic ischemia caused by small ischemic lesions would be likely.

Morphological brain tissue damage caused by microembolic air introduced through intra-arterial angiography has

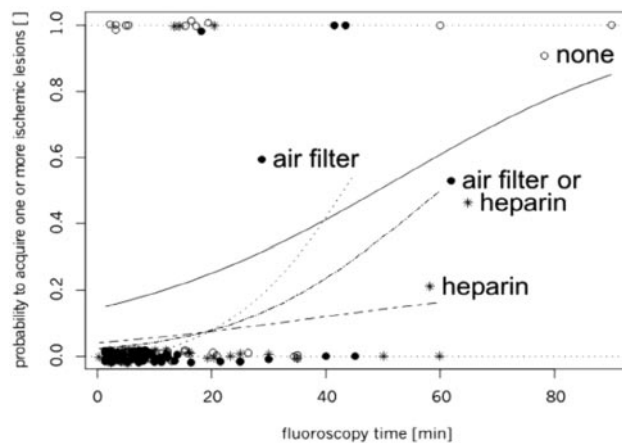


Figure 4. Nonparametric logistic regression plots of fluoroscopy time (minutes) vs probability to develop 1 or more ischemic lesions. Study groups were examined with conventional IA-DSA (open circle), or with IA-DSA plus air filters (solid circle), or with heparin (*). Note that either treatment reduces angiographic risk for ischemia, but lesion probability increases with fluoroscopy time in all treatment groups. Although air filtering is more beneficial if total fluoroscopy time is short, heparin treatment has a stronger protective effect, with above-average fluoroscopy times. Curves represent logistic estimates for different procedures. Symbols denote actual figures from study.

been demonstrated histologically.²⁵ A large number of microembolic signals in the cerebral vessels has been described not only during cerebral angiography⁹ but also during cardiologic intra-arterial procedures.^{25,26} This finding has been attributed primarily to tiny air bubbles introduced by contrast medium or flushing solution.^{9,26,27} In the present study, we identified 2 patterns of MES: single MESSs, which occurred during all phases of angiography, and MES showers, which were related exclusively to injections of contrast medium. Similar findings have been reported by others.¹⁰ Single MESSs may represent air bubbles introduced by the catheter flushing or guidewire exchanges, whereas MES showers are probably caused by tiny air bubbles dissolved in the contrast medium, especially if the contrast syringe is drawn up swiftly. As in previous studies,^{9,26,27} we could not identify a relation between MESSs and neurological deficit. However, patients with ischemic lesions on MRI revealed more single MESSs, whereas the duration of MES showers that occurred during injections of contrast medium did not differ. This finding suggests that these potentially relevant air emboli leading to subsequent ischemic lesions may be associated with guidewire manipulations or catheter flushing rather than by injections of contrast medium. Beyond circumscribed ischemic

TABLE 3. Median Single MES Count, Median Duration of MES Showers (ms), and Number of Ischemic Lesions on DW-MRI

	Heparin	Air Filter	Control
Median single MES, n (range)	44 (2–165)	29 (0–112)	66 (4–286)
Median MES shower, s (range)	40 (0–177)	5 (0–52)	57 (4–198)
Ischemic lesions on DW-MRI, n	4	4	17

Median number and range of single MES count (top), median duration and range (ms) of the MES showers (middle), and overall number of ischemic lesions (bottom) in the heparin, air filter, and control groups.

lesions, there is also a potential clinical impact on cognitive functions, as described in cardiac surgery patients. In the extracorporeal circulation, some authors have found a correlation between cognitive impairment and the number of MESs,^{28–30} with a reduction by use of air filters on the arterial line.²⁸ However, others did not confirm this association between MESs and neuropsychological deficits,³¹ and neuropsychological benefits of off-pump cardiac surgery have not been shown unequivocally.³²

In the light of these findings, a reduction of either thrombofibrinous or gaseous MESs seems worthwhile. Nevertheless, the benefit in terms of neurological and neuropsychological functions needs to be elucidated.

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