One-year outcome of the sevoflurane in acute myocardial infarction randomized trial

Résultats à un an du sévoflurane dans une étude randomisée sur l'infarctus aigu du myocarde

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Abstract

Background Sevoflurane is an inhalation anesthetic that has cardioprotective effects. There is limited information regarding its use outside of the operating room and its potential protective effect for patients presenting with myocardial infarction.

Methods In the Sevoflurane In Acute Myocardial Infarction trial, patients with a first acute ST-elevation myocardial infarction (STEMI) who were treated by primary percutaneous coronary intervention were randomized to inhalation of sevoflurane or oxygen (control). From the time of the patient's arrival for cardiac catheterization, the anesthesia team administered sevoflurane or oxygen for 30 min using a tight-fitting mask.

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The manufacturers of the anesthetic products had no role in the study.

Authors' contributions Shahar Lavi and Ronit Lavi contributed to the conception and design of the study. Shahar Lavi contributed to data analysis and drafted the manuscript. Mistre Alemayehu contributed to the acquisition of data during cardiac catheterization. David McCarty contributed to the acquisition of echocardiography data and analysis. James Warrington contributed to the acquisition of nuclear imaging data and analysis. Ronit Lavi contributed to overall trial management. Mistre Alemayehu, David McCarty, James Warrington, and Ronit Lavi contributed to the writing of the manuscript.

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In this substudy, we report the one-year outcomes. Patients were followed clinically for one year; they underwent a thallium cardiac viability study at six months and an echocardiogram at one year.

Results Forty-six patients completed follow-up. One patient in the sevoflurane group died. The mean [standard deviation (SD)] ejection fraction by single-photon emission computed tomography at six months was 51.7 (7.7)% in the sevoflurane group and 51 (9.1)% in the control group (mean difference, 0.7%; 95% confidence interval [CI], −5.9 to 7.3; $P = 0.831$). The median [interquartile range] amount of scarring at six months was 0% [0 - 8] in the sevoflurane group and 2.5% [0 - 7.1] in control group (mean difference, −0.1%; 95% CI, −4.6 to 4.4; $P = 0.700$). The mean (SD) percentage of hibernating myocardium was similar in both groups 0% [0, 5] (mean difference, −1.3%; 95% CI, −3.4 to 0.9; $P = 0.259$). The mean (SD) ejection fraction at one year increased compared with baseline by 8.0 (9.1)% ($P < 0.001$).

Conclusions In this study, we did not find an effect of sevoflurane on left ventricular function or myocardial injury at one year post STEMI. This trial was registered at www.clinicaltrials.gov; identifier: NCT00971607.

Résumé

Contexte Le sévoflurane est un anesthésique inhalé qui a des effets cardioprotecteurs. On ne dispose que de peu

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d'informations sur son utilisation en dehors du bloc opératoire et sur son effet protecteur potentiel chez les patients ayant un infarctus du myocarde.

Méthodes Dans l'étude *Sevoflurane In Acute Myocardial Infarction* (sévoflurane dans l'infarctus aigu du myocarde), des patients ayant un premier infarctus avec élévation du segment ST (STEMI) qui avaient été traités par intervention coronaire percutanée primitive ont été randomisés en deux groupes selon qu'ils recevaient une inhalation de sévoflurane ou d'oxygène (groupe contrôle). À partir du moment de l'arrivée du patient en salle de cathétérisme, l'équipe d'anesthésie administrait du sévoflurane ou de l'oxygène pendant 30 minutes au moyen d'un masque étroitement ajusté. Dans cette sous-étude, nous décrivons les résultats à un an. Les patients ont été suivis cliniquement pendant une année; ils ont bénéficié d'une étude de viabilité cardiaque au thallium à 6 mois et un échocardiogramme à 1 an.

Résultats Quarante-six patients ont terminé le suivi. Un patient du groupe sévoflurane est décédé. La fraction d'éjection moyenne (écart-type [ET]) mesurée par tomographie d'émission monophotonique à six mois était de 51,7 % (7,7 %) dans le groupe sévoflurane et 51 % (9,1 %) dans le groupe contrôle (différence des moyennes: 0,7 %; intervalle de confiance [IC] à 95 %: -5,9 à -7,3; $P = 0,831$). La quantité médiane [intervalle interquartile] de tissu cicatriciel à six mois était de 0 % [0 - 8] dans le groupe sévoflurane et 2,5 % [0 - 7,1] dans le groupe témoin (différence des moyennes: -0,1 %; IC à 95 %: -4,6 à 4,4; $P = 0,700$). Le pourcentage moyen (ET) de myocarde en hibernation était comparable dans les deux groupes: 0 % [0, 5] (différence des moyennes: -1,3 %; IC à 95 %: -3,4 à 0,9; $P = 0,259$). La fraction d'éjection moyenne (ET) à un an a augmenté comparativement aux valeurs de référence de 8,0 % (9,1 %) ($P < 0,001$).

Conclusions Au cours de cette étude, nous n'avons pas trouvé d'effet du sévoflurane sur la fonction ventriculaire gauche ou sur la lésion myocardique, un an après un infarctus du myocarde avec élévation du segment ST. Cette étude a été enregistrée sur le site www.clinicaltrials.gov; identifiant: NCT00971607.

There are two major goals in the treatment of patients with myocardial infarction (MI), namely, improving their outcome and alleviating their discomfort. The most important factor affecting cardiovascular outcome in the setting of ST-elevation myocardial infarction (STEMI) is rapid restoration of myocardial reperfusion, which is typically achieved by primary percutaneous coronary intervention (pPCI).¹ When pPCI is not readily available, administration of a thrombolytic agent is a reasonable

alternative. In both scenarios, there is need for adjunctive therapy to reduce ischemic and reperfusion injury.² A major goal in cardiovascular disease research is the search for adjunctive intervention or medication.

One potential mechanism to reduce ischemia-reperfusion injury involves ischemic conditioning.³ Several studies performed in the setting of STEMI have shown the effectiveness of this intervention.^{4,5} However, other recent studies, including a study published by our group, did not show clinical benefit from ischemic conditioning, suggesting that the precise mode of applying ischemic conditioning should be explored further.^{6,7} In particular, it seems that it is important to apply the ischemic conditioning intervention as early as possible. Administration of a pharmacological agent that mimics ischemic conditioning can be initiated early and may be suitable for all patients with STEMI receiving reperfusion therapy, including fibrinolysis and pPCI.

Restoration of coronary blood flow is frequently associated with improvement in symptoms, but there is usually a need for adding sedatives and analgesia.⁸ Therefore, adding an agent with sedative/analgesic properties that also has a potential to reduce ischemia-reperfusion injury is an attractive option.

The volatile anesthetic sevoflurane is such a potential pharmacological agent.⁹ When compared with intravenous anesthesia, sevoflurane has been shown to reduce the incidence of MI and intensive care unit stay, the length of time on mechanical ventilation following cardiac surgery, in-hospital mortality, and long-term cardiac events.¹⁰⁻¹⁴ The effect of sevoflurane as a cardioprotective agent has not been shown in all studies,¹⁵ and results were also dependent on duration of administration, number of exposures, and dose. For instance, in one study, the beneficial effects were observed only when administered throughout the surgery and not when administered in a fashion similar to ischemic conditioning, before cardiopulmonary bypass, or following the creation of the coronary anastomosis.¹⁶ Therefore, some of the beneficial effects may have been related to the effect on myocardial oxygen supply-demand balance and not due to an effect of pharmacological conditioning. Administration of sevoflurane during coronary artery bypass graft surgery was also associated with a reduction in late cardiac events.¹⁷ Several meta-analyses showed that volatile anesthetics were associated with a reduction in postoperative troponin release, although not all showed an effect on clinical outcome.^{15,18} It is possible that volatile anesthetics have a different cardioprotective effect in patients not undergoing heart surgery.¹⁹

Therefore, to explore a potential cardioprotective effect of sevoflurane during pPCI, we performed the *Sevoflurane In Acute Myocardial Infarction* (SIAMI) trial. The short-

term outcomes were previously reported.²⁰ Our objective for the current study was to determine the influence of sevoflurane vs intravenous sedation during pPCI on left ventricular (LV) function as assessed by single-photon emission computed tomography (SPECT) imaging six months following the procedure. Further, as a *post hoc* analysis, we assessed the degree of scarring and hibernating myocardium at six months and LV function by echocardiography at one year.

Methods

The Research Ethics Board of Western University approved the study in March 2009. All patients provided written informed consent prior to enrolment. The study is registered at www.clinicaltrials.gov; identifier NCT00971607.

Study population

The design of the SIAMI study was previously published along with the primary outcome.²⁰ This was a single-centre, randomized, double-blind, controlled trial. Enrolment criteria included patients who were aged 18–75 yr, presenting within six hours of onset of chest pain with a first STEMI, and referred for pPCI. In addition, patients had to have symptoms lasting > 30 min and an electrocardiogram showing ST-segment elevation > 0.1 mV in two or more contiguous leads. Exclusion criteria included: cardiac arrest, cardiogenic shock, previous MI, previous coronary artery bypass surgery, pre-infarction angina, heart failure (New York Heart Association class III/IV), chronic inflammatory disease, known severe renal impairment, hepatic dysfunction, use of glibenclamide, and a history of self or familial malignant hyperthermia. Recruitment for the study began in May 2009 and ended in October 2012. Follow-up was completed in October 2013.

Procedural interventions and randomization

Percutaneous coronary intervention was performed according to standard clinical practice and utilizing approved devices. Patients received dual antiplatelet therapy, including acetylsalicylic acid and a loading dose of clopidogrel. Anticoagulants and GPIIb/IIIa inhibitors were administered according to the cardiologists' discretion. Patients were randomized 1:1 to sevoflurane or control using a computer-generated randomization sequence in random blocks of 8, 12, and 16. The randomization sequence and envelopes were prepared by an administrative assistant. Participants were enrolled by

the cardiac catheterization team and randomized consecutively according to the envelope number. The anesthesia team members who received the sealed randomization envelope were not blinded to the study drug and assisted in the administration of other intravenous medications, including midazolam and fentanyl. All other team members, including the interventional cardiologist, the cardiac catheterization lab, and coronary care unit nurses were blinded to the study drug. Data were collected and analyzed in a blinded fashion.

Sedation protocol (intervention and comparator groups)

During the procedure, an anesthesia gas machine with a standard anesthesia circuit, a gas scavenging system, and monitoring according to the Canadian Anesthesiologists' Society²¹ and American Society of Anesthesiologists' guidelines were used. The anesthesiologist administered sevoflurane with a mixture of oxygen and air through a tight-fitting mask. The mask was applied immediately after the beginning of standard monitoring and prior to PCI. The sevoflurane group received 50% oxygen and sevoflurane. Sevoflurane (or oxygen) was given for 30 min or until completion of PCI, whichever occurred first. The tight-fitting mask was removed after 30 min. All patients in the control group received 50% oxygen by a similar mask connected to the anesthesia machine and sedation by intravenous midazolam. Patients in the sevoflurane group could receive standard sedatives, including midazolam, in addition to sevoflurane. Patients in both groups could receive fentanyl if needed. The sevoflurane target mean alveolar concentration (MAC) was 0.5, as it was previously reported that low dose provides protection against ischemia-reperfusion injury in humans.²² Sevoflurane MAC levels were monitored continuously. As a safety measure and in order to provide similar sedation to the control group, the depth of sedation was monitored continuously using bispectral index (BIS), with a target BIS value of 80.

Study endpoints

The objectives of the current study were to assess the effect of pharmacological conditioning with sevoflurane on myocardial function and viability at six months, as well as LV function and the incidence of death, MI, and repeat revascularization after one year post STEMI.

²⁰¹Thallium single-photon emission computed tomography (SPECT)

The study was performed six months post MI. Patients were administered 111–148 MBq of thallium-201 chloride

intravenously followed by gated tomographic imaging with CT attenuation correction on Infinia Hawkeye 4TM SPECT/CT gamma cameras (GE Healthcare) equipped with low-energy high-resolution or low-energy all-purpose collimation. A 10% energy window was centred at 70 keV, and a 15% energy window was centred at 160 keV. Patients were imaged in the supine position with their arms elevated above their heads. A 180° non-circular orbit was employed, and a 64x64 image matrix was used. Three sets of images were acquired following tracer injection: immediately, at four hours, and at 24 hr. A motion correction algorithm was applied to tomographic image reconstruction when required. Infarct size and hibernating myocardium were calculated as previously described.^{23,24} A physician blinded to patient randomization read the single-photon emission computed tomography tests.

Echocardiography assessment

Patients underwent assessment of LV function by echocardiography at baseline, usually the day following pPCI, and after one year. Two-dimensional and Doppler echocardiography were performed in a standard fashion.²⁵ Segmental wall motion was assessed as recommended by the American Society of Echocardiography and scored from 1 (normal) to 4 (dyskinetic), and the wall motion score index was calculated. The LV ejection fraction (EF) was calculated according to Simpson's rules. A technician and a physician blinded to patient randomization read the echocardiographic studies.

Statistical analysis and power calculation

Continuous baseline variables are summarized by mean (standard deviation; SD) or median (interquartile range [IQR]) if not normally distributed, and categorical variables are summarized by counts (percentages). Comparisons between continuous variables were performed using Student's *t* test or Wilcoxon rank-sum test where appropriate. Categorical variables were compared with the Pearson Chi square test. A paired Student's *t* test was used to compare the one-year ventricular ejection fraction with baseline in both groups combined. Subgroup analysis and adjustments according to location of the infarct (anterior vs non-anterior) were predefined. All reported *P* values are two sided.

The SIAMI study was originally powered for a 35% reduction in infarct size as assessed by measurement of the area under the curve of creatine kinase, which is similar to other initial studies of ischemic or pharmacological conditioning.^{20,26,27} With a statistical power of 80% and a type I error of 0.05 using a two-sided test, we needed to enrol 50 patients. The sample size calculation was

performed for the primary outcomes, which were reported previously, and not for the secondary outcomes that are reported here.

Results

Fifty patients were randomized; however, three patients found to have acute pericarditis and not a MI were excluded from the study.²⁸ One patient relocated out of the country and was lost to follow-up. Forty-six patients completed the one-year clinical outcome assessment. The study flow diagram is shown in Fig. 1. Baseline characteristics of the patients included in the follow-up study are presented in Table 1, and the procedural characteristics of patients who completed one year of follow-up are presented in Table 2. There were no significant differences between the groups in any of the baseline variables. Two patients, one from each group, underwent urgent coronary artery bypass graft surgery during the initial admission. Use of GPIIb/IIIa inhibitors and aspiration catheters were similar in both groups. At discharge, all patients received acetylsalicylic acid, clopidogrel, statins, angiotensin-converting enzyme inhibitors, and beta blockers.

During one year of follow-up, none of the patients had recurrent MI. One patient in each group required repeat revascularization, and one patient in the sevoflurane group died. Thirty-three patients completed the SPECT study, and 37 underwent echocardiography at one year.

The median [IQR] amount of scarring on the thallium study performed six months post MI was low in both groups: 0% [0 - 8] in the sevoflurane group and 2.5% [0 - 7.1] in the control group (mean difference, -0.1%; 95% confidence interval [CI], -4.6 to 4.4; *P* = 0.700). The mean (SD) percentage of hibernating myocardium was similar in both groups 0% [0, 5] (mean difference, -1.3%; 95% CI, -3.4 to 0.9; *P* = 0.259) (Fig. 2).

Left ventricular function as assessed by echocardiogram within two days of admission showed a mean (SD) EF of 44.7 (9.3)% in the sevoflurane group and 46.8 (7.8)% in the control group (mean difference in LV ejection fraction [LVEF], -2.1%; 95% CI, -7.3 to 3.1; *P* = 0.423). Mean (SD) left ventricular ejection fraction by SPECT at six months was 51.7 (7.7)% in the sevoflurane group and 51.9 (9.1)% in the control group (mean difference, 0.7%; 95% CI, -5.9 to 7.3; *P* = 0.831). At one year, the mean (SD) EF by echocardiogram was 54.8 (7.1)% in the sevoflurane group and 53.9 (7.1)% in the control group, with no significant difference between the groups (mean difference in LVEF, 0.9%; 95% CI -3.9 to 5.6; *P* = 0.716) (Fig. 3). Overall, the mean (SD) EF increased in all study patients after one year by 8.0 (9.1)% compared with baseline (*P* <

Fig. 1 Study flow diagram

Table 1 Baseline characteristics of patients included in long-term follow-up

	Sevoflurane (n = 24)	Control (n = 22)
Age—yr	62 (12)	62 (11)
Female sex	5 (21%)	5 (23%)
Smokers	6/24 (25%)	11/21 (52%)
Hypertension	14/24 (58%)	15/22 (68%)
Dyslipidemia	12/23 (52%)	8/22 (36%)
Diabetes mellitus	3/24 (13%)	5/22 (23%)
Body mass index—kg·m ⁻²	27.3 (3.7)	29.0 (5)
Systolic blood pressure—mmHg	144 (27)	150 (32)
Heart rate—beats·min ⁻¹	78 (13)	76 (18)
First contact to 1 st device—min	78 (23)	79 (22)
Creatinine baseline—μMol·L ⁻¹	80 (22)	81 (22)

Data represent mean (SD) or number (%)

0.001). There was no difference between groups in terms of change from baseline ($P = 0.284$).

Half of the patients presented with anterior MI. Among the anterior MI group, there was a non-statistically significant trend towards a larger relative increase in mean (SD) EF by echocardiography in the sevoflurane group vs the placebo group [41.7 (38.0)% vs 20.2 (15.4)%, respectively; $P = 0.173$] and less scarring [4.5 (7.3)% vs 10.5 (6.6)%, respectively; $P = 0.169$]. Even though these differences were not statistically significant, the magnitude

of the observed benefit may be large enough to warrant further investigation.

Discussion

We have previously shown that administration of low-dose sevoflurane during pPCI is an effective method for sedation of patients presenting with STEMI.²⁰ We found an initial improvement in ST-segment elevation resolution, a marker of reperfusion and a predictor of cardiovascular outcomes. Nevertheless, the primary endpoint, namely, infarct size assessed by the area under the curve of creatine kinase and troponin, was not different between the groups.²⁰

In the current study, there were no significant differences in clinical or imaging outcomes between the groups during one year of follow-up with the same patients.

There are several potential reasons to explain the lack of effect of sevoflurane on long-term outcome in this study. First, both groups of patients experienced a favourable outcome. There were just a few clinical events, and overall LV function was good. The good outcome reflects contemporary management of patients with STEMI that includes rapid transfer for pPCI and effective medical therapy, including dual antiplatelet agents, frequent use of GPIIb/IIIa inhibitors, and contemporary anticoagulants.

Indeed, the time from first contact to first device in our patients was < 80 min. Further, due to the nature of our trial and its complexity and in accordance with the

Table 2 Characteristics of percutaneous coronary and anesthesia procedure

	Sevoflurane (n= 24)	Control (n = 22)
Infarct-related artery		
Left anterior descending	15/24 (63%)	8/22 (36%)
Right coronary	6 (25%)	10 (45%)
Circumflex artery	4 (17%)	3 (14%)
Intermediate artery	0	1 (5%)
Baseline TIMI flow		
0	15 (63%)	12 (57%)
1	0	2 (10%)
2	4 (17%)	2 (10%)
3	5 (21%)	5 (24%)
Final TIMI flow		
0	1 (4%)	0
1	0	1 (4.5%)
2	0	0
3	23 (96%)	21 (95%)
Use of aspiration catheter	14 (58%)	12 (55%)
Anesthesia		
BIS	83.7 (6.2)	84.9 (2.7)
Anesthesia time (min)	61 (23)	61 (23)
Midazolam use	6 (25%)	21 (95%)
Fentanyl use	11 (46%)	18 (82%)
MAC (%)	0.32 (0.12)	0
Drugs given during PCI		
Unfractionated heparin	23 (96%)	18 (81%)
Bivalirudin	0	3 (14%)
GPIIb/IIIa inhibitors	22/24 (92%)	19/22 (86%)

Data represent mean (SD) or number (%)

BIS = bispectral index; MAC = mean alveolar concentration; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction

inclusion and exclusion criteria, we enrolled lower risk patients such as those presenting with a first MI, in a stable hemodynamic condition, and at a relatively young age. Consequently, our study was underpowered to detect differences in clinical outcomes.

Patients in both groups could receive fentanyl as part of standard analgesia for MI. More fentanyl was required in the control group. Opioids have been reported to provide cardioprotection, and therefore, the use of fentanyl may have masked a potential protective effect of sevoflurane.²⁹

It is also possible that the protective effect of sevoflurane seen in animal models and in some of the human studies does not apply to patients presenting with MI. Such an effect may also be reduced in patients with diabetes.³⁰

Other parameters assessed during the initial hospital admission, in particular the degree of myocardial injury,

Fig. 2 Thallium results, scarring (a) and hibernating myocardium (b). Median is 0 and 75th percentile is upper line **Fig. 3** Left ventricular ejection fraction at one year; lines represent mean and standard deviation

were not different between the sevoflurane and control groups.²⁰

One question that needs to be addressed in the design of pilot studies assessing myocardial protecting agents is targeting the population that will most likely benefit from the studied therapy while maintaining a broad enough study population to allow reasonable recruitment and generalizability of the study results. In order to achieve maximal effect, we began administering the study drug prior to coronary angiography.³¹ With this approach, the patients benefited from the effective sedation provided by the anesthesia team, and we avoided selection of patients

according to angiographic findings. Nevertheless, this approach resulted in the inclusion of patients with MI who did not have an occluded artery and even a few patients without an MI. This design had a negative effect on the power of our study. Further, patients with larger infarcts or those with an anterior MI are more likely to benefit from such an intervention.^{5,6,27,32}

Indeed, in our initial study, there was a trend toward a stronger effect of sevoflurane in patients with an anterior MI on assessing myocardial injury by release of cardiac enzymes.²⁰ In the current study, we did not observe an overall clinically meaningful effect of sevoflurane on the long-term assessment of LV function, myocardial scarring, or hibernating myocardium. These findings align with the modest effect on the short-term outcomes. Based on our findings, we cannot recommend sevoflurane sedation as a means of myocardial protection during STEMI.

Limitations

This was a small pilot study in which sevoflurane was given for the first time to patients presenting with STEMI; therefore, it was difficult to estimate the clinical effect of sevoflurane. As with other studies in which the initial informed consent is obtained during the acute phase, some patients later decided not to continue with all tests and this had a negative effect on the results and power of the study. In the sevoflurane group, there was a higher proportion of anterior MI. This could have been avoided if we were to stratify randomization according to infarct location. We used a low dose of sevoflurane to provide light sedation and potentially cardioprotection. We cannot exclude the possibility that a higher dose would be more effective in cardioprotection. Patients in both groups had excellent outcome, and therefore, it is difficult to detect significant differences with such study results. It is possible that mild differences between groups could have been detected if we had used a more sensitive imaging technology such as cardiac magnetic resonance imaging.

As a result, future studies should focus on higher risk patients and include a larger sample size and sensitive imaging modalities.

In summary, we did not find an effect of sevoflurane on LV function or myocardial injury within one year post pPCI for STEMI.

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Conflicts of interest None declared.

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