Non-invasive evaluation of new-onset atrial fibrillation after cardiac surgery: a protocol for the BigMap study

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Abstract

Aims New-onset atrial fibrillation (NOAF) is the most common complication after cardiac surgery, occurring in 25–50% of patients. It is associated with post-operative stroke, increased mortality, prolonged hospital length of stay, and higher treatment costs. Previous small observational studies have identified the left atrium as a source of the electrical rotors and foci maintaining NOAF, but confirmation by a large prospective clinical study is still missing. The aim of the proposed study is to investigate whether the source of NOAF lies in the left atrium. The correct identification of NOAF-maintaining structures in cardiac surgical patients might offer potential therapeutic targets for prophylactic perioperative ablation strategies.

Methods and results This is a prospective single-centre observational study of patients developing NOAF after cardiac surgery. The primary outcome is the description of NOAF-maintaining structures within the atria. Key secondary outcomes include overall mortality, intensive care unit length of stay, hospital–ventilator-free days, and proportion of persistent NOAF. In NOAF patients, the non-invasive electrophysiological mapping will be conducted using a 252-electrode electrocardiogram vest. After mapping, a low-dose computed tomography scan of the chest will be performed to integrate the electrophysiological mapping results into a 3D picture of the heart. The study will include approximately 570 patients, of whom 30% (n = 170) are expected to develop NOAF. Sample size calculation revealed that 157 NOAF patients are necessary to assess the primary outcome. Patients will be tracked for a total of 5 years.

Conclusions This is the largest prospective study to date describing the electrophysiological mechanisms of NOAF using non-invasive mapping.

Keywords Cardiac surgery; New-onset atrial fibrillation; Non-invasive cardiac mapping; Cardiac surgical critical care

Introduction

Atrial fibrillation (AF) is the most commonly observed post-operative complication after cardiac surgery. Its incidence ranges from 25% to 50% [25% after isolated coronary artery bypass grafting (CABG), 30% after isolated valvular procedures, and 40–50% after combined procedures]. Although new-onset atrial fibrillation (NOAF) is usually self-limiting, it leads to increased early mortality and stroke, prolonged intensive care unit (ICU) and hospital stays, and higher treatment costs. Furthermore, recent data show that NOAF increases the long-term risk for cerebrovascular events after CABG. After cardiac surgery, data about structures triggering AF are scarce because the onset is usually within the first 48 to 96 post-operative hours. Furthermore, invasive electrophysiological examination after cardiac surgery is...
time-consuming and potentially harmful in the early post-operative phase and, thus, not feasible in daily practice. Several factors have been identified to increase the risk of NOAF: (i) vasoactive agents used for haemodynamic stabilization,6,8 (ii) poor post-operative pain control,9 and (iii) post-operative fluid overload.10,11 Additional factors contribute to the local myocardial inflammation due to reperfusion injury after cardiopulmonary bypass.12 First, the frequent transfusion of blood products presents a potent inflammatory stimulus.10,13 Second, metabolic alterations, especially perioperative hyperglycaemia, jeopardize myocardial cell membrane integrity and induce oxidative injury, both of which contribute to the inflammatory response.14,15 Third, the presence of pericardial blood also induces local irritation and inflammation, resulting in significant inflammatory processes and consecutively increasing the risk for NOAF.16 Fourth, de novo acute kidney injury, another common complication after major cardiac surgery, may lead to electrolyte disorders, metabolic alterations, and large volume shifts, all of which are potent triggers of AF.17,18 Finally, procedures including atriotomy have shown to increase local inflammation and alter atrial conduction in animal models.19

Nevertheless, the exact location of structures triggering or maintaining NOAF remains unknown. NOAF is presumably caused by rapidly firing foci or rotors (re-entrant circuits) within the atria.19 In a small observational study, Swartz et al. found evidence of NOAF resulting from left atrial foci to be associated with local myocardial fibrosis.20 These results are supported by a randomized controlled trial where perioperative pulmonary vein isolation did not reduce the incidence of NOAF.21 Identifying the exact location of NOAF-maintaining foci and rotors could allow development of preventive treatment strategies such as preoperative or perioperative ablation of high-risk structures. However, assessing the exact location of NOAF-maintaining structures briefly after cardiac surgery by an invasive electrophysiological examination is logistically questionable. Non-invasive phase mapping, on the other hand, allows description of AF foci and rotors using a 252-electrode vest applied to the patient’s torso and enables detailed mapping of NOAF-maintaining structures without the need for invasive electrophysiological examination. In a small retrospective study, Ehrlich et al. demonstrated the feasibility of non-invasive phase mapping of NOAF after cardiac surgery.22 The proposed study aims to correctly identify the exact location of structures triggering or maintaining NOAF in patients who develop this complication after cardiac surgery with the use of non-invasive phase mapping.

Study design

The Basel CardiOInsight™ Mapping (BigMap) study is an investigator-initiated, single-centre, prospective, non-randomized observational study of patients who develop NOAF after cardiac surgery. This study will be performed by the Department of Cardiac Surgery, the Intermediate Care Unit, and ICU at the University Hospital Basel, Basel, Switzerland.

This study aims to describe the exact location of NOAF-maintaining foci and rotors. We hypothesize that NOAF is primarily maintained by structures of the left atrium (Figure 1; Regions 1, 2, 3, and 6 according to Haissaguerre).23

Study objectives

The primary outcome measure is localization of foci and rotors maintaining NOAF after cardiac surgery identified by non-invasive phase mapping and a low-dose computed tomography (CT) scan of the chest. Localization of the foci and rotors will be described according to Haissaguerre et al. (Figure 1).23

Secondary outcome measures (Table 1) include major adverse cardiac events including overall mortality, incidence of stroke/transient ischaemic attack, myocardial infarction, and critical care parameters such as ventilator-free days and hospital-free days. Hospital-free days are defined as the number of days a patient stays outside of a hospital beginning at study inclusion and continuing until death or end of follow-up. Ventilator-free days at 28 days are defined as the number of days between successful weaning from mechanical ventilation and Day 28 after inclusion. In the event of mechanical ventilation for >28 days or death before completion of 28 days, ventilator-free days will be counted as zero.25 Table 1 provides an overview of the secondary objectives assessed in the NOAF cohort and the control group.

An overview of baseline patient data, assessment tools, and investigated parameters and predictors for NOAF in our cohort of cardiac surgical patients is provided in Table 2.

Study population

The study will focus on patients who develop NOAF after cardiac surgery in whom we will perform the non-invasive mapping procedure (investigative group). A second group, including patients without NOAF, will serve as a control group. We will differentiate between inclusion/exclusion criteria for study inclusion and for the mapping procedure as follows:

General inclusion criteria

Participants fulfilling the following inclusion criteria are eligible for the study:

- Adult patient (≥18 years of age)
- Elective cardiac surgery
- Signed informed consent by patient or next of kin
General exclusion criteria

Participants meeting the following criteria are excluded from the study:

Preoperative conditions:

- History of previous left atrial ablation
- Pregnant or lactating women
- History of cardioembolic stroke
- History of amiodarone treatment during the last 3 months
- Any documented history of AF/atrial flutter before surgery
- Left ventricular ejection fraction < 40%
- Inclusion in another study involving radiation exposure

Perioperative conditions:

- Perioperative mechanical circulatory support [e.g. intra-aortic balloon pump; extracorporeal membrane oxygenation; and left ventricular assist device (e.g. Impella, Abiomed Inc., Aachen, Germany)]

Mapping inclusion criteria

- NOAF developing on the cardiac surgery ward, intermediate care unit, or ICU of the University Hospital Basel within the first 7 post-operative days (168 h) after cardiac
surgery. ICU admission will be set as starting point for the observation period.

**Mapping exclusion criteria**

Heart rate \( \geq 50 \) b.p.m. AND contraindication to adenosine. 
Contraindications to adenosine:

- Known allergy/intolerance to adenosine
- History of chronic obstructive pulmonary disease (GOLD IV)\(^{26}\)
- History of asthma
- History of long-QT syndrome
- Haemodynamically unstable patients (margin of discretion of the attending physician)

**Recruitment and inclusion**

Ongoing recruitment of elective patients by the study team members will be performed during daily practice. All patients referred to the Department of Cardiac Surgery, University Hospital Basel, are routinely informed about the potential complication of NOAF and about the BigMap study. All patients who agree to participate in the study will be required to sign an informed patient consent form. We will include all screened cardiac surgical patients \( \geq 18 \) years of age who agree to participate and who do not fulfil any exclusion criteria.

**Study procedure**

Beginning at ICU admission until the end of the study period (168 h of observation), the patient’s cardiac rhythm will be continuously monitored on the ICU using telemetry and on the ward with routine 12-channel electrocardiogram (ECG). ECG recordings demonstrating the presence of continuous AF lasting \( \geq 5 \) min will be declared as having NOAF, as in previous trials assessing NOAF\(^{21,27–30}\) (Figure 2A).

As part of the mapping procedure (Figure 3), a CardioInsight™ (CIT) cardiac mapping vest (Medtronic Switzerland, Tolochenaz, Switzerland) will be applied to patients who have consented to the mapping procedure and present with NOAF. CIT is a non-invasive single-beat cardiac phase mapping system that provides three-dimensional electroanatomic maps of the heart. During the mapping process, the CIT system acquires and processes the ECG recordings from the vest, allowing for the visualization of cardiac atrial and ventricular anatomy in real-time. This technology aids in identifying potential arrhythmogenic substrates and can guide further diagnostic and therapeutic interventions.
procedure, it is essential to lower the patient’s heart rate to <50 b.p.m. for a few seconds. The rationale is to avoid ventricular potentials that may superimpose over atrial potentials. To achieve this, a single 6–18 mg rapid intravenous bolus of adenosine will be administered to patients as a single rapid intravenous bolus. Adenosine [Krenosin®, Sanofi-Aventis (Suisse) SA, Vernier, Switzerland] is a nucleotide that is mainly used to terminate atrioventricular re-entry tachycardia. It has a good safety profile due to its ultra-short half-life. Its main pharmacologic effect is on the atrioventricular node, where it blocks atrioventricular conduction for a few seconds. The adenosine application will slow the patient’s heart rate and allow for correct mapping using the CIT device. Patients contraindicate for adenosine
(allergy/intolerance, asthma, chronic obstructive pulmonary disease GOLD IV, and long-QT syndrome) will be excluded from mapping only but not from the cohort study. As this non-invasive mapping can be performed within a few minutes, the clinical management of NOAF will not be critically delayed.

Consecutively, a low-dose thoracic CT scan (neck to upper abdomen) will be performed independent from the patient’s cardiac rhythm. This investigation can be delayed in justified cases for a maximum of 480 min according to the manufacturer’s instructions. In addition, the CT scan will follow a standardized protocol as pre-defined by the manufacturer of the CIT vest (Figure 2B).

Patient follow-up including current rhythm information, medical history, current medical therapy, and complications of NOAF including stroke or transient ischaemic attack, neurologic outcome assessment using Modified Rankin Scale, overall mortality, ventilator-free days, hospital-free days, permanent pacemaker or implantable cardioverter defibrillator implantation, and myocardial infarction will be performed after 90 days and 1, 3, and 5 years (Table 1).

The overall duration of this study is expected to last 7 years. This includes a 2 year recruitment phase and data collection at the above-described intervals until 5 year follow-up. Included patients will have the opportunity to withdraw consent at any time during the study without any negative effects on their medical treatment. Figure 2A and Supporting Information, Table S1 provide an overview of the timeline of the planned procedures.

**Statistics**

**Sample size calculation**

We chose a precision-based approach to derive a suitable sample size, as we are not evaluating different groups of patients; hence, there is no natural hypothesis of difference between groups. We expect all localizations to be effectively
the same, given the homogeneous phenotype of the study cohort. In order not to be underpowered in case some localizations are different, we assume a prevalence of 90% of the left atrium maintaining NOAF. It is possible that non-invasive mapping as a diagnostic tool will not yield the correct result in each case considering the fact that timing and exact placement of the electrodes are crucial. Hence, there is a possibility for false negatives and it makes sense to implement this source of uncertainty as sensitivity of non-invasive mapping as diagnostic method. We assume a sensitivity of 90%. To achieve a precision of 95% confidence interval (CI) of 0.1157, patients will be needed to accomplish an 84–94% CI (Table 3). If the prevalence of NOAF from the left atrium is substantially lower, we will have to accept a broader CI. With a prevalence of 80% and a sensitivity of 75%, 157 patients will yield a CI width of 0.15. In total, we will include 170 patients with NOAF to account for dropouts. If the relevance of the left atrium in maintaining NOAF can be confirmed after recruitment of 85 patients, fewer patients will be needed to achieve a precision CI width of 0.15. In case the first 85 patients present with the left atrium as the source of NOAF, we can achieve a CI of 81–95% assuming a sensitivity of 0.9.

Table 3 Precision-based sample size calculation to determine the number of participants needed to achieve a certain confidence width

| Prevalence | Sensitivity | CI width 0.1 | CI width 0.15 | CI width 0.2 |
|------------|-------------|---------------|---------------|---------------|
| 0.6        | 0.70        | 533           | 234           | 130           |
| 0.75       | 476         | 210           | 116           | 66            |
| 0.80       | 407         | 180           | 100           | 53            |
| 0.85       | 327         | 145           | 81            | 42            |
| 0.90       | 235         | 107           | 61            | 32            |
| 0.95       | 139         | 68            | 42            | 28            |
| 0.7        | 0.70        | 457           | 201           | 111           |
| 0.75       | 408         | 180           | 100           | 53            |
| 0.80       | 349         | 154           | 86            | 46            |
| 0.85       | 280         | 124           | 70            | 32            |
| 0.90       | 202         | 92            | 53            | 28            |
| 0.95       | 119         | 58            | 36            | 21            |
| 0.8        | 0.70        | 400           | 176           | 97            |
| 0.75       | 357         | 157           | 87            | 46            |
| 0.80       | 306         | 135           | 75            | 32            |
| 0.85       | 245         | 109           | 61            | 28            |
| 0.90       | 177         | 80            | 46            | 21            |
| 0.95       | 104         | 51            | 32            | 15            |
| 0.9        | 0.70        | 356           | 156           | 87            |
| 0.75       | 318         | 140           | 78            | 41            |
| 0.80       | 272         | 120           | 67            | 28            |
| 0.85       | 218         | 97            | 54            | 21            |
| 0.90       | 157         | 71**          | 41            | 15            |
| 0.95       | 93          | 46            | 28            | 15            |

CI, confidence interval.
*Reading example 1: If the prevalence of the pulmonary vein causing atrial fibrillation is 0.6 and sensitivity is 0.9, 107 patients are needed to achieve a 95% confidence interval (CI) as narrow as 0.8 to 0.95, hence a CI of width 0.15.
**Reading example 2: If the prevalence of the pulmonary vein causing atrial fibrillation is 0.9 and sensitivity is 0.9, 71 patients are needed to achieve the same CI.

**Primary analysis**
The primary goal of this study is to localize the areas of the atria responsible for maintaining NOAF in afflicted patients after cardiac surgery. Data analysis will be descriptive with particular focus on multiple localizations in the same patient.

**Secondary analysis**
Should the study reveal that left atrium is not the structure maintaining NOAF in >10% of cases, we will consider investigating predictive factors for localization among patient-related and surgery-related variables using logistic regression. These factors would have to be tested in a larger cohort of sequential cardiac surgical patients who did or did not develop NOAF.

**Interim analysis**
We plan to assess the prevalence of the left atrium’s role as an essential structure maintaining NOAF after investigating 85 patients. As there is no randomization, thus no blinding, the interim analysis will not require the help of a second statistician. Furthermore, the sample size calculation was based on precision; therefore, it does not need to be increased to avoid type II error.

**Deviation(s) from the original statistical plan**
Details on the relevant structures maintaining NOAF are so far unknown. It might be that the typical result of CIT assessment is diffuse with no source to be identified, which would preclude data analysis in a strict sense.

**Data sharing and publication**
There will be no public access to the data during the ongoing study until publication. We will perform an interim analysis and prepare a publication for submission to peer-reviewed journal after inclusion of 85 patients. In addition, we plan further peer-reviewed publications of our findings after completion of the 90 day and 1, 3, and 5 year follow-ups.

**Safety analysis and serious adverse events**
The application of adenosine might lead to serious adverse events (SAEs) due to haemodynamic instability associated with bradycardia. To maximize patient safety during the mapping procedure, patients will be investigated in an environment with the possibility for immediate advanced cardiac life support and continuous monitoring. As adenosine has an ultra-short half-life, we do not expect any sustain haemodynamic effects. Patient transport after mapping to perform the CT scan is another a potential risk for SAEs. As a precaution, every ICU patient will be escorted by a physician and a critical care nurse.

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**Ethics and registration**

This study complies with the Declaration of Helsinki, and the study protocol has been approved by the local Ethics Committee of Northwestern and Central Switzerland (Project-ID 2021-01353). This study is registered at ClinicalTrials.gov (www.clinicaltrials.gov, identifier: NCT04964765).

**Discussion**

To our knowledge, the BigMap study is the first large observational study to assess NOAF in adult cardiac surgical patients using non-invasive mapping. The incidence of AF increases with reduced ejection fraction, and it is known that heart failure and AF predispose each other. As the aim of this study is to describe pure NOAF, we decided to investigate a homogenous patient cohort with no additional predisposing factors. The primary outcome of this study aims to detect the structures that maintain NOAF after cardiac surgery using high-quality data provided by non-invasive phase mapping technology. We hypothesize that the left atrium maintains NOAF in >90% of patients after cardiac surgery. As secondary outcome measures, we plan to prospectively identify potential risk factors for the development of NOAF with a long-term follow-up of 5 years.

In a small pilot study, Ehrlich et al. demonstrated the feasibility of non-invasive mapping after cardiac surgery. Ten patients with NOAF after cardiac surgery underwent non-invasive mapping and were compared with 10 control group patients who had evidence of long-standing persistent AF before surgery and underwent preoperative non-invasive mapping followed by a Cox-Maze III/IV procedure. The findings of this pilot study support our hypothesis, as Ehrlich et al. demonstrated that the main rotor regions were in the left atrial appendage, the interatrial groove, and the pulmonary vein area (Bordeaux classification, Regions 1–3) in both groups. Although right atrial rotor activity was also found in both groups, this is only a pilot study and a description of exact localization of rotors in NOAF in larger prospective studies is currently missing.

Although NOAF is also documented in non-cardiac surgery patients, the incidence is significantly lower than in cardiac surgery, indicating a possible role of the surgical trauma to the heart and the detrimental effects of extracorporeal circulation. While isolated CABG shows the lowest incidence in NOAF, incidences of up to 50% were observed in mitral valve or combined surgery.Various therapeutic strategies to reduce the incidence of NOAF have been described. Nevertheless, the incidence of post-operative AF has been not unchanged over the last decades. The most common prophylactic and therapeutic approaches include the post-operative administration of beta-blockers or amiodarone as well as the correction of electrolytes, especially potassium and magnesium. Patients with long-term or multiple NOAF events are often treated with oral anticoagulation, a treatment that comes with the high burden of complications. The risk of perioperative stroke is approximately two-fold higher for patients with NOAF compared with controls, and recent guidelines support the increased risk associated with NOAF.

As existing studies have mainly focused on the management of NOAF, the BigMap study follows a new approach. For the first time, non-invasive phase mapping allows low-risk electrophysiological mapping within the first post-operative days after cardiac surgery. The BigMap study will primarily describe the relevant anatomical structures responsible for maintaining NOAF. It will secondarily assess a variety of NOAF predictors and risk factors in a cohort study after various cardiac surgical procedures with planned follow-ups up to 5 years. This study plans to include 170 patients who develop NOAF within the first 7 post-operative days and 570 patients with no diagnosed NOAF who will serve as a control.

We hypothesize that NOAF mainly arises in the left atrium of affected adult patients after cardiac surgery. The results of the BigMap study will eventually allow the development of prophylactic preoperative or perioperative ablation strategies to reduce morbidity and mortality caused by NOAF.

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**Conflict of interest**

David Santer has received speaker honoraria and educational grants from Abbott and Medtronic as well as speaker honoraria from Abiomed and Nycomed GmbH. Michael Kühne reports personal fees from Bayer, Boehringer Ingelheim, Pfizer, BMS, Daiichi Sankyo, Medtronic, Biotronik, Boston Scientific, and Johnson&Johnson and grants from Bayer, Pfizer, Boston Scientific, BMS, and Biotronik. The other authors report no potential conflict of interest relevant to this study.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Timeline of study conductance.

| Event | Date |
|-------|------|
| Study initiation | 2009 |
| Randomization | 2010 |
| Data collection | 2011 |
| Data analysis | 2012 |
| Publication | 2013 |

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