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CARDIOPLEGIA AND VENTRICULAR LATE POTENTIALS IN CARDIAC SURGICAL PATIENTS

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Schütz N, Romand J-A, Yanez ND, Treggiari MM, Bendjelid K. Cardioplegia and ventricular late potentials in cardiac surgical patients. This work has been performed in the Division of Intensive care, Department of Anaesthesiology, Pharmacology and Intensive Care, Geneva University Hospitals.
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ABSTRACT. Background and objective. Ventricular late potentials (LP) recording with signal-averaged electrocardiogram allow identifying patients at risk of sudden death and ventricular tachycardia. Cardiac surgery with cardiopulmonary bypass (CPB) could predispose to the development of myocardial ischemia related to imperfect cardioplegia. To the best of our knowledge, no study investigated the protection of cardioplegia and CPB regarding the occurrence of LP in patients without previous myocardial infarction and undergoing cardiac surgery. **Methods.** In 61 elective patients scheduled for cardiac surgery involving CPB, signal-averaged electrocardiogram was performed the day before and 24–48 h after the surgery. The electrodes were positioned according to Frank's orthogonal derivations. Twenty five patients were excluded because of poor quality signals, leaving 36 patients (age, 64 ± 14) available for the analyses. An abnormal signal-averaged electrocardiogram was considered when ≥2 of the recorded indexes were present. McNemar's tests were performed on the dichotomized values to investigate differences in pre-post scores. **Results.** The mean CPB duration was of 110 ± 57 min. Patients scheduled for cardiac surgery do not exhibited LP after CPB (no significant difference in pre-post CPB scores, P = NS). The probability of a patient with a negative score transitioning to a positive score was 0.23 (P = NS). **Conclusions.** The present study in cardiac surgical patients suggests that cardioplegia associated to CPB has no significant impact on the occurrence of LP, irrespective of surgery performed.

KEY WORDS. arrhythmias, heart surgery, perioperative ischemia.

INTRODUCTION

Ventricular tachycardia and fibrillation are the primary mechanisms of sudden death after recovery from myocardial infarction [1–5]. Numerous studies attempted to identify patients at risk for such complications with non-invasive techniques. Ventricular tachyarrhythmia (VT) has been associated with the presence of slow and inhomogeneous action potential conduction in several myocardiopathies (coronary disease, congenital myocardiopathies) [6–9]. Since 20 years, these conduction abnormalities are usually detected non invasively through the use of a signal-averaged surface electrocardiogram (SAECG) that consists of low-amplitude-high frequency

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signals recording of the terminal portion of the QRS complex (termed late potentials; LP) [10, 11].

Cardiopulmonary bypass (CPB) allows circulatory assistance during cardioplegia induced cardiac arrest and permits to achieve optimal surgical conditions. It was speculated that the resulting cardiac resting state could be associated with transient ischemia. Indeed, some authors attributed the occurrence of interventricular septal motion asynchrony in the post operative setting [12, 13] to a probable myocardial ischemic suffering. Even if SAECG lacks of clinical relevance to predict the outcome of patients with CABG [14], this technique could be a valuable tool to prove the safety of cardioplegia, since the occurrences of LP could be a feature of ischemic arrhythmogenic substrate.

To the best of our knowledge no study investigated the safety of CPB and cardioplegia regarding the occurrence of LP in patients without previous myocardial infarction and undergoing cardiac surgery involving CPB. The present study aimed to respond to the current question.

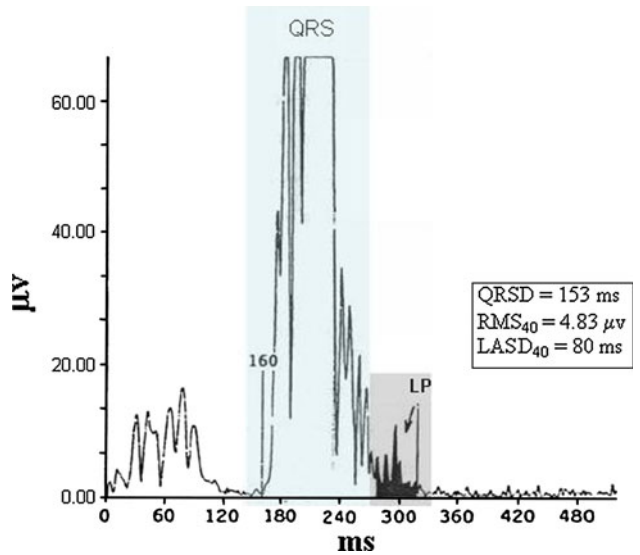

Fig. 1. Figure displaying an abnormal signal-averaged surface electrocardiogram (SAECG; positive late potential; LP). QRSD QRS duration, $LASD_{40}$ duration of low amplitude signals of > 40 ms, RMS_{40} voltage of signals of the last 40 ms of the QRS complex.

MATERIALS AND METHODS

The study was approved by the ethical committee of the institution [Central Ethical Committee 03-077-APSIC 03-004 of Geneva University Hospitals, Geneva, Switzerland]. All patients gave written consent. Patients were eligible if they were scheduled for elective cardiac surgery and further admitted in surgical intensive care unit.

Three groups of patients were identified according to the type of procedure: valvular surgery, coronary artery bypass graft (CABG) surgery or both. This stratification was done to independently evaluate the effect of CPB and cardioplegia on patients with and without coronary disease (and thus ischemic substrates). Exclusion criteria were patients with previous history of myocardial infarction, right and/or left bundle branch blocks (QRS > 120 ms), an ejection fraction less than 40%, a medical history of ventricular tachycardia and patients taking antiarrhythmic agents.

Signal-averaged electrocardiograms

A signal-averaged ECG (SAECG; CARDIOVIT CS-200, SCHILLER, Reomed AG, Dietikon, Switzerland) was performed the day before and 24–48 h after the surgery. The electrodes were positioned according to Franck's orthogonal derivations. Standard orthogonal bipolar leads (X, Y, and Z) were used. 200 beats signals were amplified, digitized, averaged and then filtered using a bi-directional Butterworth 40–250 Hz band pass filter. LP filtering was accepted when noise levels were ≤ 0.4 µV. Analog to digital conversion was performed with a sampling rate of 2,000 Hz. The present analysis conforms to standards issued by the Task Force Committee of the European Society of Cardiology, the American Heart Association and the American College of Cardiology [15].

The duration of the filtered QRS complex, the duration of the low-amplitude (< 40 µV) signals in the terminal portion of the QRS and the root-mean square (RMS) voltage of the terminal 40 ms of the filtered QRS complex were recorded. An abnormal SAECG was defined when ≥2 of the following indexes were present: a total QRS duration of > 114 ms, low-amplitude signals (LAS; < 40 µV) duration > 40 ms and a RMS voltage of signals in the last 40 ms of the QRS complex < 20 µV (Figure 1). Moreover all patients had a normal electrocardiogram (ECG) performed before and after surgery. All measurements were performed by the same investigator and were independently verified by another investigator not involved in the data collection.

Perioperative management

Usual medications, except for diuretics and angiotensin-converting enzyme inhibitors or angiotensin-II antagonists, were administered on the morning of the procedure. Premedication consisted in subcutaneous morphine sulfate

0.1 mg kg^{-1}. In the operating room, catheters were inserted in a peripheral vein, the right jugular vein and the radial artery of the non-dominant arm. Standard monitoring was applied including: pulse oximetry, leads II and V5 of the ECG for heart rate (HR) and automated ST-segment trend analysis, continuous measurements of mean arterial and central venous pressures (MAP and CVP, respectively), nasopharyngeal temperature, end-tidal capnography, bispectral analysis of the EEG (BIS Aspect Medical Systems A-2000 XP) as well as transesophageal echocardiography (Philips Sonos 5500, Philips Medical Systems, Andover, MA).

A balanced anaesthetic technique included sufentanyl (a bolus of 0.5–0.9 μg kg^{-1} followed by 0.4–0.8 μg kg^{-1} h^{-1}), etomidate (0.2 mg kg^{-1} for anaesthesia induction), midazolam (0.1 mg kg^{-1} h^{-1} for anaesthesia maintenance) and pancuronium. In the three groups (valvular surgery, CABG surgery and both), a similar depth of anaesthesia was achieved by targeting BIS values between 40 and 60. After full heparinization (300 IU/kg), cardiopulmonary bypass (CPB) was instituted using non-pulsatile flow (2.2–2.5 l/min/m^2), mild hypothermia (32°–34°C) and alpha-stat control for acid–base management. The circuit and the membrane oxygenator were primed with 1 l of lactate-ringer solution mixed with 1 l of hydroxyethyl starch (HAES Steril) and mean arterial pressure (MAP) was targeted between 50 and 70 mmHg with pharmacological manipulation as necessary. Myocardial protection was achieved by antegrade infusion of hyperkaliemic blood solution (4°C, 20 mEq potassium) followed by cold blood re-infusion through the ascending aorta after a 30 min period. After aortic closure and re-warming up to a rectal temperature ≥35.5°C, a nitroglycerin infusion was started (2 mg h^{-1}) and weaning from bypass was guided by echocardiographic assessment and standard hemodynamic measurements. The pump flow was gradually reduced while the heart was progressively filled in order to optimize the preload-recruitable stroke volume and to reach a MAP ≥70 mmHg. Optimal cardiac filling was judged by achieving a maximal left ventricular diameter in the short-axis view of 2.5–2.8 cm m^{-2} and vasodilators (nitroglycerine, nitroprussiate) or vasopressors (phenylephrine, norepinephrine) were titrated to maintain MAP between 70 and 90 mmHg. The heart was electrically paced if it failed to maintain a heart rate ≥70 beats/min. Inotropes were not routinely administered during weaning from CPB. The threshold for blood transfusion was a haematocrit value less than 18% during CPB and less than 25% after CPB; or higher values (26–30%) if associated with hemodynamic instability and/or ECG signs of myocardial ischemia. After surgery, patients were transferred to the intensive care unit. Cardiac enzymes dosages were performed as clinically indicated after the surgical procedure.

Statistical analysis

Descriptive analyses were performed on the original scores (i.e., levels 0, 1, 2, 3), and on the dichotomized values of the original scores. The original scores were transformed as follows: patients' scores of 0 or 1 were classified as negative (0); patients' scores of 2 or 3 were classified as positive (1). The data were analysed, stratified by operation type: valve (Group 1), coronary (Group 2), both valve and coronary (Group 3). We also performed a combined analysis of all data (i.e., ignoring surgery type). Our primary hypothesis was that there was no significant difference in post–pre scores for patients undergoing valve surgery. Our secondary hypotheses were: (a) there was no significant difference in post–pre scores for patients receiving the coronary operation; (b) there was no significant difference in post–pre scores for patients receiving both the valve and coronary operation; (c) there was no significant difference in post–pre scores for all patients (ignoring surgery type). The data were paired and collected at the patient level. McNemar's test was performed on the dichotomized values to investigate whether there were differences in post–pre scores among the three surgery types combined. We would conclude that the post–pre scores are not significantly different if the upper and lower limits of our 90% confidence interval on the paired differences does not exceed ±0.055. Under the assumption that a 5.5% difference in the pre-post probabilities reflects equivalence, we would conclude the two probabilities are equivalent if the estimated confidence interval for the difference is fully contained inside the interval (−0.055, 0.055). We used an exact 90% confidence interval obtained from McNemar's procedure to account for the paired binary data for our test of equivalence [16].

RESULTS

In 61 elective patients scheduled for cardiac surgery involving CPB, 25 patients were excluded because of poor quality signals, leaving 36 patients available for the analyses. Mean noise after signal averaging was 0.2–0.4 μV. Demographic data of the 36 patients included are presented in Table 1. All patients had a pre and post-operative SAECG. A total of 36 pre and post-operative SAECG were analysed. Seventeen patients without coronary lesions were underwent valve surgery (11 aortic valve only, four mitral valve only and two aortic and

Table 1. Demographic data of patients

n of patients	36
Mean age (years)	64 ± 13
Valve surgery (*n*)	17
Coronary surgery (*n*)	8
Valve and coronary surgery (*n*)	11
Mean CPB duration (min)	110 ± 57
Mean aortic clamp time (min)	78.5 ± 35.7
Mean LVEF (%)	62 ± 11

CPB cardiopulmonary bypass, *LVEF* left ventricular ejection fraction.

mitral valve combined). Eight patients underwent CABG and 11 both CABG and valve surgery. All surgeries were performed using CPB. Among patients with CABG, the mean number of the diseased coronary vessels was of 2 ± 1 and the mean left ventricular ejection fraction was of 62 ± 11%. 20 patients had a reported systemic hypertension. The mean CPB duration was of 110 ± 57 min, and the mean aortic clamp duration was of 78.5 ± 35.7 min. Postoperative biochemical markers of ischemia and EKG didn't reveal any subclinical myocardial injury in all patients.

Table 2. Two-by-two table of paired binary data for pre and post patients late potential scores

	Pre LP	Pre No LP	Total
Post LP	4	6	10
Post No LP	6	20	26
Total	10	26	36

In the present study no relationship was observed between gender and LP. Moreover, no relationship was observed between the occurrence of LP and echo-parameters such as left posterior wall thickness and intra-ventricular septum thickness. There were no differences in pre and post scores comparing surgeries with or without coronary disease, or all surgeries combined. For our hypothesis, part c., the data are displayed in Table 2. The 90% confidence interval (CI) on post—pre difference was −0.186, 0.186. Based on these estimates, if the sample was 10 times larger, the 90% CI for the post—pre difference would be −0.053, 0.053, which would be contained in the a priori defined interval of equivalence.

There was no post scores of three or higher (Table 3). Based on the dichotomized scores, we estimated that the probability of a subject with a negative score remaining negative is approximately 0.77. The probability of a person with a negative score transitioning to a positive score was 0.23. Patients originally classified as positive are less likely to remain positive (0.40) and more likely to be classified as negative (0.60).

DISCUSSION

The present study confirmed that patients without coronary disease undergoing valve surgery do not exhibited LP after CPB (i.e., there was no significant difference in pre-post CPB scores, NS). Likewise, patients with coronary disease undergoing CABG with or without valve surgery did not develop LP after CPB.

Since its initiation in the 1950s, CPB has revolutionised cardiac surgery, allowing ever more complex procedures to be undertaken. This technique provides adequate

Table 3. Pre- and post-operative SAECG scores of all patients

	Post CPB							
	All data				Valve surgery			
	0 Post-operative score	1 Post-operative score	2 Post-operative score	Total	0 Post-operative score	1 Post-operative score	2 Post-operative score	Total
0	15	0	6	21	7	0	3	10
1	4	1	0	5	2	0	0	2
2	4	1	4	9	3	1	1	5
3	1	0	0	1	–	–	–	–
Total	24	2	10	36	12	1	4	17

As example, six patients with 0 preoperative scores developed a score of two following CPB. No patient exhibited an SAECG score of three after surgery.

support to vital organs and to the heart while the surgeon is working on bloodless heart for a protracted duration. The present study suggests that this modality of cardioplegia associated to CPB is safe and has no impact on the occurrence of LP after cardiac valve surgery. Fragmented QRS complexes (and more precisely LP of the QRS complex) have traditionally been used as a marker of conduction abnormality in several cardiomyopathies, and specially in the setting of ischemic heart disease [17–19] and then as a substrate of malignant tachyarrhythmia. LPs are low amplitude signals that occur in the ventricles. These signals are caused by slow or delayed conduction of the ventricular activation sequence. Under certain abnormal conditions, there may be small regions of the ventricles within a diseased or ischemic region that generate such delayed conduction. This results in depolarization signals that prolong past the refractory period of surrounding tissues and re-excite the ventricles. This re-excitement is known as ''re-entry''. Re-entry is believed to be a key factor that causes LPs and is a feature of ventricular arrhythmias.

Because, we frequently observe paradoxical transitory interventricular septal motion abnormalities on transthoracic echocardiography after cardiac surgery [12, 13], also in patients undergoing valve surgery, some authors hypothesized that cardioplegia-induced ischemia could be responsible for this phenomenon. Indeed even if the hyperkaliemic cardioplegia is traditionally employed to afford myocardial protection and increase ventricular performance, this latter has been associated with significant cardiomyocyte swelling and reduced contractility, representing a possible mechanism of myocardial stunning [20]. Moreover, the level of troponin-I, troponin-T and CK-MB release after CPB-technique heart surgery is significantly correlated with the mean CPB and aortic cross-clamp times [21]. However, our data suggest that cardioplegia associated to CPB is safe and has no significant impact on the occurrence of LP, irrespective of surgery performed.

The present study has limitations. First, we were unable to obtain electrocardiographic signal averaging after the discharge of the hospital, in order to evaluate the long term course of the potentials recorded during the perioperative period. Second, anaesthetics such as isoflurane and sevoflurane could also have protective effects on cardiac function after CPB, as supported by several prior studies [22].

In conclusion, the present study contributes to our understanding of cardioplegia protection using subclinical measures of electrical myocardial injury. These data suggest that there was no subclinical myocardial injury as indicated by the absence of occurrence of LP in patients undergoing cardiac surgery with the use of CPB.

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