Smoking has a significant impact on patients with FMD. Diagnosis of FMD may have been delayed in patients who had ever smoked, because symptoms could have been attributed to smoking-related disease. Smokers with FMD had significantly higher rates of claudication, aneurysm, and need for therapeutic intervention. Of note, therapeutic interventions for non-FMD indications were excluded from analysis, and the arteries on which therapeutic interventions were performed were consistent with the arterial beds with FMD involvement. Thus, atherosclerosis is not the driver of therapeutic interventions in smokers with FMD. Smokers also tended to have an increase in the prevalence of major vascular events (42.8% vs 36.8%, p = 0.077). A multivariate logistic regression adjusting for age at diagnosis, sex, and other characteristics also did not show statistical significance (odds ratio: 1.16; 95% confidence interval: 0.86 to 1.57; p = 0.34). Lack of statistical significance could reflect the lack of power to detect this association in a cohort of 949 patients with FMD.

The high prevalence of aneurysms is concerning. Although it is well known that smoking is associated with aneurysms, smoking also appears to increase the risk for aneurysms in patients with FMD, a population in which the risk for aneurysmal disease is already significant (4). Screening for intracranial aneurysms in all patients with FMD is recommended (5); however, the method of screening for aneurysm in other vascular beds is yet undefined. The recently published scientific statement on FMD (5) lists the creation of a vascular screening approach for patients with FMD as a top research priority. The present study emphasizes the importance of screening, particularly for aneurysm, and particularly in patients with histories of smoking.

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REFERENCES

Superior Myocardial Protection Using “Polarizing” Adenosine, Lidocaine, and Mg2+ Cardioplegia in Humans

Myocardial protection with current methods of cardioplegia is still incomplete (1–3). Several studies have shown that hyperkalemic solution may lead to cell injury (1,2). Adenosine-lidocaine-magnesium (ALM) is a new normokalemic, “polarizing” method of cardioplegia that arrests the heart at its resting membrane potential (1). Pre-clinical studies have shown ALM to provide improved protection compared with hyperkalemic solutions (1,2). A recent clinical trial also observed improved outcomes with ALM-enriched hyperkalem ic cardioplegia (3). We hypothesized that normokalemic, “full-polarizing” ALM microplegia from induction to reanimation provides improved myocardial protection compared with hyperkalemic arrest (3).

After institutional review board approval was obtained, 208 patients requiring elective, isolated, low-risk coronary artery bypass graft surgery or aortic valve replacement were prospectively enrolled and provided informed consent. Patients were randomized to standard 4:1 Buckberg cardioplegia (3) (104 patients; high-K⁺ group) or full-polarizing ALM microplegia (104 patients; ALM group). ALM microplegia had...
physiological $[K^+]$ in the arrest/induction bolus (5 mEq/l; reference range: 3.5 to 5.0 mEq/l), and in the high-$K^+$ group, $K^+ > 15$ mEq/l (3). The primary efficacy endpoint was troponin I, measured before anesthetic induction (T0), at intensive care unit (ICU) admission (T1), at the 6th hour post-operatively (T2), and at the 18th hour post-operatively (T3). Using a superiority design, with 80% power and an alpha value of 5%, 100 patients per arm were required to detect a 20% troponin I difference at T2 (high-$K^+$ group, mean $5.1 \pm 2.5 \ \mu g/l$) (3). Coronary sinus troponin I, lactate, venous oxygen saturation (SvO$_2$), and base excess (BE) were measured before aortic cross clamping (T0cs) and 10 min after aortic-declamping (T1cs). The “myocardial anaerobic index” was calculated from coronary sinus lactate/SvO$_2$.

Secondary endpoints were cardiac index, indexed systemic vascular resistance, pulmonary capillary wedge pressure, indexed pulmonary vascular resistance, and central venous pressure, collected pre-operatively (T0), at the end of cardiopulmonary bypass (T1), at ICU admission (T2), at the 6th hour post-operatively (T3), and at the 18th hour post-operatively (T4).

European System for Cardiac Operative Risk Evaluation scores were low and comparable in the 2 groups (ALM group $1.6 \pm 0.9\%$ vs. high-$K^+$ group $1.7 \pm 0.9$, p = 0.58); similarly, the percentage of patients undergoing coronary artery bypass graft surgery and aortic valve replacement was similar (ALM group 78 [75%] and 26 [25%] vs. high-$K^+$ group 72 [69.2%] and 32 [30.8%], p = 0.35). ALM induction required 34 s longer to cardiac arrest (162 vs. 128 s, p = 0.03). After declamping, 79% of ALM patients spontaneously returned to sinus rhythm, compared with 48% in the high-$K^+$ group (p < 0.001). Aortic cross-clamping time (ALM group $53.0 \pm 18.4$ min vs. high-$K^+$ group $52.2 \pm 19.9$ min, p = 0.78) and cardio-pulmonary bypass time (ALM group 75.4 ± 25.2 min vs. high-$K^+$ group 79.9 ± 24.3 min, p = 0.18) were comparable. In the ALM group, coronary sinus troponin I and lactate were lower and SvO$_2$ and BE comparable. In the ALM group, coronary sinus troponin I and lactate were lower and SvO$_2$ and BE higher: troponin I (ALM group T0cs 0.9 ± 0.7 µg/l and T1cs 1.3 ± 0.7 µg/l vs. high-$K^+$ group T0cs 0.9 ± 1.0 µg/l and T1cs 2.3 ± 2.6 µg/l, p = 0.002), lactate (ALM group T0cs 1.0 ± 0.4 mmol/l and T1cs 1.5 ± 0.5 mmol/l vs. high-$K^+$ group T0cs 0.9 ± 0.3 mmol/l and T1cs 1.8 ± 0.5 mmol/l, p < 0.001), SvO$_2$ (ALM group T0cs 51.4 ± 10.8% and T1cs 62.9 ± 12.3% vs. high-$K^+$ group T0cs 53.2 ± 12.2% and T1cs 51.1 ± 11.5%, p < 0.001), and BE (ALM group T0cs 0.5 ± 2.8 and T1cs –0.1 ± 1.4 vs. high-$K^+$ group T0cs 0.7 ± 3.0 and T1cs –0.9 ± 2.2, p = 0.001). In the ALM group, the myocardial anaerobic index at reperfusion was lower than in the high-$K^+$ group (0.02 ± 0.02 vs. 0.04 ± 0.01, p = 0.001, between-group p = 0.003). Coronary sinus $[K^+]$ in the ALM group was significantly lower at reperfusion (3.9 ± 0.4 mEq/l vs. high-$K^+$ group

### TABLE 1: Biochemical and Hemodynamic Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Time Points</th>
<th>Time p Value</th>
<th>Group p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical data*</td>
<td></td>
<td>T0</td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td>Troponin I (µg/l)</td>
<td>ALM</td>
<td>0.02 ± 0.02</td>
<td>3.9 ± 1.1</td>
<td>5.0 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>High K</td>
<td>0.01 ± 0.02</td>
<td>5.2 ± 4.2</td>
<td>6.3 ± 3.2</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>ALM</td>
<td>0.9 ± 0.2</td>
<td>1.1 ± 0.3</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>High K</td>
<td>0.8 ± 0.2</td>
<td>1.5 ± 0.7</td>
<td>1.2 ± 0.6</td>
</tr>
<tr>
<td>CV parameters†</td>
<td></td>
<td>T0</td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>ALM</td>
<td>1.4 ± 0.3</td>
<td>1.8 ± 0.4</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>High K</td>
<td>1.4 ± 0.3</td>
<td>1.5 ± 0.3</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>ALM</td>
<td>8.6 ± 3.1</td>
<td>8.5 ± 4.0</td>
<td>11.7 ± 5.7</td>
</tr>
<tr>
<td></td>
<td>High K</td>
<td>8.6 ± 3.6</td>
<td>10.4 ± 6.8</td>
<td>14.5 ± 7.0</td>
</tr>
<tr>
<td>ISV (dyne/sec/cm²/m²)</td>
<td>ALM</td>
<td>3.58 ± 1.01</td>
<td>2.97 ± 1.40</td>
<td>3.503 ± 1.165</td>
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<td></td>
<td>High K</td>
<td>3.682 ± 1.128</td>
<td>3.174 ± 866</td>
<td>3.602 ± 929</td>
</tr>
<tr>
<td>IPVR (dyne/sec/cm²/m²)</td>
<td>ALM</td>
<td>329.6 ± 209.8</td>
<td>350.8 ± 197.1</td>
<td>308.9 ± 163.9</td>
</tr>
<tr>
<td></td>
<td>High K</td>
<td>351.8 ± 229.6</td>
<td>384.3 ± 227.4</td>
<td>332.3 ± 240.7</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>ALM</td>
<td>6.9 ± 4.3</td>
<td>7.6 ± 4.5</td>
<td>10.6 ± 5.3</td>
</tr>
<tr>
<td></td>
<td>High K</td>
<td>5.6 ± 4.2</td>
<td>6.9 ± 4.2</td>
<td>9.4 ± 4.3</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *Biochemical time points: T0 — before anesthetic induction; T1 — intensive care unit admission; T2 — 6th hour post-operatively; T3 — 18th hour post-operatively. CV time points: T0 — pre-operatively; T1 — end of cardiopulmonary bypass; T2 — intensive care unit admission; T3 — 6th hour post-operatively; T4 — 18th hour post-operatively. †Time-group interaction (p < 0.0001) for lactate.

ALM = adenosine-lidocaine-magnesium; CI = cardiac index; CV = cardiovascular; CVP = central venous pressure; high K = Bublberg cardioplegia; IPVR = indexed pulmonary vascular resistance; ISVR = indexed systemic vascular resistance; PCWP = pulmonary capillary wedge pressure.
Further multicenter trials are in the planning stages.

5.8 ± 0.4 mEq/l, p = 0.012) and remained within normal reference values. When “peak” troponin I was considered, the following distribution was observed in patients: 1) ≤50 × 99th percentile upper reference limit (URL) = ALM group 24% versus high-K⁺ group 34.6%; 2) 50 to 100 × 99th percentile URL = ALM group 6.7% vs. high-K⁺ group 5.8%; 3) 100 to 150 × 99th percentile URL = ALM group 59.6% vs. high-K⁺ group 21.2%; and 4) >150 × 99th percentile URL = ALM group 9.6% vs. high-K⁺ group 38.5% (p < 0.001). Peripheral blood troponin I and lactate were significantly lower after ALM, with an improved “cardiodynamic” pattern (Table 1). There were no acute myocardial infarctions or hospital deaths. Perioperative low-cardiac output syndrome (3.8% in the ALM group vs. 4.8% in the high-K⁺ group, p = 0.75), inotropic support (p = NS), and length of hospitalization (8.2 ± 4.1 days vs. high-K⁺ group 8.1 ± 2.9 days, p = 0.78) were similar. A shorter ICU stay was reported after ALM (27.2 ± 13.5 h vs. 36.6 ± 26.1 h, p < 0.01).

High-potassium arrest has been the standard of care in cardiac surgery for decades (1). The present study is the first prospective, randomized human trial examining fully polarized “normokalemic” blood ALM cold cardioplegia. Previous studies relate to “substrate enrichment” of K⁺-based depolarizing solutions with membrane-polarizing substances (1-3). We report that normokalemic ALM cardioplegia led to superior cardioprotection on the basis of: 1) significantly higher spontaneous return to sinus rhythm; 2) significantly lower coronary sinus troponin I, lactate, and K⁺ at reperfusion; and 3) significantly lower peripheral blood troponin I and lactate with improved cardiac index during the first 18 h (Table 1). These benefits were associated with 1 less day in the ICU. ALM was also associated with lower myocardial anaerobic index at reperfusion, indicating improved oxygen-based ATP support of cardiac work in a normokalemic environment, consistent with a higher BE and less myocardial acidosis (4).

In summary, this prospective randomized trial shows that normokalemic “polarized” ALM cardioplegia is safe and efficacious in elective surgery. Further multicenter trials are in the planning stages.

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**REFERENCES**


**Antihypertensive Drug Usage in Prediction of Incident Atrial Fibrillation**

*A Factor Not to Be Disregarded*

The Dutch PREVEND (Prevention of Renal and Vascular End-Stage Disease) cohort study (1) reported both the risk factors for atrial fibrillation (AF) and the association of AF with cardiovascular events, heart failure, and all-cause mortality. At a mean 9.7 years of follow-up of more than 8,000 middle-aged men and women, 265 cases of AF were confirmed. A greater focus was given to associations with outcome than to determinants of AF, perhaps because no unexpected factors were perceived by the investigators to emerge. However, one of the main reported findings was related to the use of antihypertensive drugs. Age- and sex-adjusted Cox regression models indicated that antihypertensive drug use was a prominent and highly significant determining variable of incident AF, with a more than 2-fold hazard ratio (HR). At 32%, antihypertensive drug use led the population-attributable risk estimates of reversible or treatable factors (i.e., beyond age and male sex), and this percentage was greater than the aggregate of the next 3 factors (previous myocardial...