

# Acupoint Catgut Embedding Reduces Insulin Resistance in Diabetic Patients Undergoing Open Cardiac Surgery

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## ABSTRACT

**Objective:** Acupoint catgut embedding (ACE) has been used safely for thousands of years in traditional Chinese medicine. The aim of this study was to assess whether ACE can improve insulin resistance and promote rapid recovery after open cardiac surgery.

**Methods:** A group of 200 patients undergoing cardiac surgery were randomly allocated to receive either ACE (ACE group) or sham ACE (SHAM group).

The primary outcome of our trial was insulin resistance assessed 1, 3, 5, and 7 days after surgery. The homeostasis model assessment (HOMA-IR) was used to measure perioperative insulin resistance. Secondary outcomes included insulin, glucose, and inflammatory cytokine (interleukin (IL) 6 and IL-8) levels; time to extubation; incidence of infection; time to first feces; acute kidney injury; incidence of postoperative nausea and vomiting (PONV); length of stay in the ICU; length of hospital stay; and other clinical parameters.

**Results:** The ACE group had lower insulin, glucose, IL-6, IL-8, and HOMA-IR levels than the SHAM group one week after the operation. The incidence of infection, incidence of PONV, time to drain removal, and length of hospital stay significantly were lower in the ACE group than in the SHAM group.

**Conclusion:** ACE can improve insulin resistance and promote rapid recovery after open cardiac surgery.

## INTRODUCTION

Insulin resistance is common in open cardiac surgery due to the surgical stress response causing the release of cortisol and catecholamines [Barth 2007]. Cardiopulmonary bypass promotes insulin resistance by increasing plasma insulin, growth hormone, glucagon, and endogenous catecholamine levels [Anand 1990]. Patients with diabetes are associated with

perioperative insulin resistance [Antonio-Villa 2020]. Therefore, patients with diabetes who undergo open cardiac surgery have severe insulin resistance and hyperglycemia postoperatively. However, perioperative hyperglycemia is known to contribute to poor outcomes, including increased morbidity and mortality, increased frequency of infection, delayed healing, postoperative delirium, acute kidney injury, and increased duration of hospital stay [Duggan 2017; Hermanides 2018]. Therefore, a stable perioperative blood glucose level is very important for patients undergoing cardiac surgery.

Intensified insulin therapies [Saager 2015] and preoperative carbohydrate drinks [Karimian 2019] are used to maintain a stable perioperative blood glucose level. However, perioperative hypoglycemia caused by intensified insulin therapy frequently occurs and is associated with adverse outcomes, including postoperative delirium, cardiac arrhythmia, increased ICU stay, and overall mortality [Investigators 2009]. Preoperative carbohydrate drinks ameliorate insulin resistance for only three days [Karimian 2019]. Therefore, it is necessary to find a method with few side effects and a long duration to maintain perioperative blood glucose stability.

Acupoint catgut embedding (ACE) has been safely used for thousands of years in traditional Chinese medicine, and it provides treatment effects in several conditions, such as

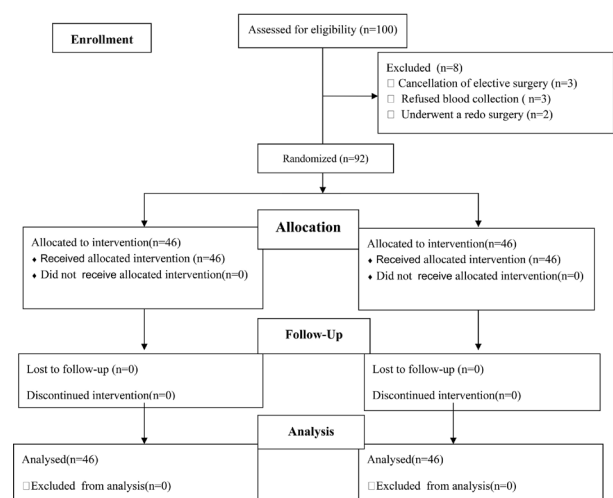


Figure 1. Patient flow diagram.

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Table 1. Patient demographics and surgical characteristics

|                                      | AEM group<br>(N = 46) | SHAM group<br>(N = 46) | P   |
|--------------------------------------|-----------------------|------------------------|-----|
| Age (years)                          | 52.3 ± 20.4           | 53.7 ± 19.6            | .63 |
| Body mass index (kg/m <sup>2</sup> ) | 21.7 ± 3.2            | 22.3 ± 3.7             | .83 |
| ASA classification (II/III)          | 24/22                 | 26/20                  | .65 |
| Duration of surgery (min)            | 176.7 ± 30.2          | 182.3 ± 25.6           | .79 |
| Size of incision (cm)                | 19.5 ± 3.7            | 20.1 ± 4.2             | .47 |
| Cardiopulmonary bypass time (min)    | 85.7 ± 21.9           | 83.5 ± 23.8            | .63 |
| Intraoperative bleeding volume (ml)  | 778.5 ± 265.7         | 798.7 ± 281.5          | .58 |
| Intraoperative urine output (ml)     | 963.7 ± 241.5         | 976.2 ± 238.4          | .79 |
| Sex (male proportion)                | 43.5%                 | 47.8%                  | .78 |
| Procedure                            | -                     | -                      | .49 |
| Mitral valve replacement             | 18                    | 20                     |     |
| Aortic valve replacement             | 28                    | 26                     |     |

obesity, refractory insomnia, and perimenopausal syndrome [Chen 2018]. Compared with manual acupuncture and electroacupuncture, ACE has the advantages of an easy operation and durable stimulation [Deng 2014]. Evidence suggests that ACE can effectively decrease blood glucose levels, enhance insulin sensitivity, and alleviate the symptoms of various complications, such as diabetes and obesity [Garcia-Vivas 2014]. However, to the best of our knowledge, randomized controlled trials of ACE in diabetic patients undergoing open cardiac surgery have not been reported. The aim of this study was to assess whether ACE can improve insulin resistance and promote rapid recovery after open cardiac surgery.

## METHODS

The current study was designed as a single-center, prospective, randomized, double-blind study and was approved by the ethics committee of the First Affiliated Hospital of Nanchang University (approval number 2019156). Written informed consent was obtained from all patients in the trial. The trial was registered before patient enrollment in the Chinese Clinical Trial Registry (ChiCTR1900026146).

## PATIENTS AND DESIGN

Enrollment was restricted to patients aged 18 to 75 years with American Society of Anesthesiologists physical status II-III undergoing cardiac surgery with a preexisting diagnosis of diabetes. Patients were ineligible if they were unable to cooperate or communicate; if they had endocrinopathy, autoimmune disease, or hepatic or renal failure; if they were undergoing secondary or urgent surgery; and if they were drug addicts. The enrolled patients were randomized into two groups: the ACE group, which received

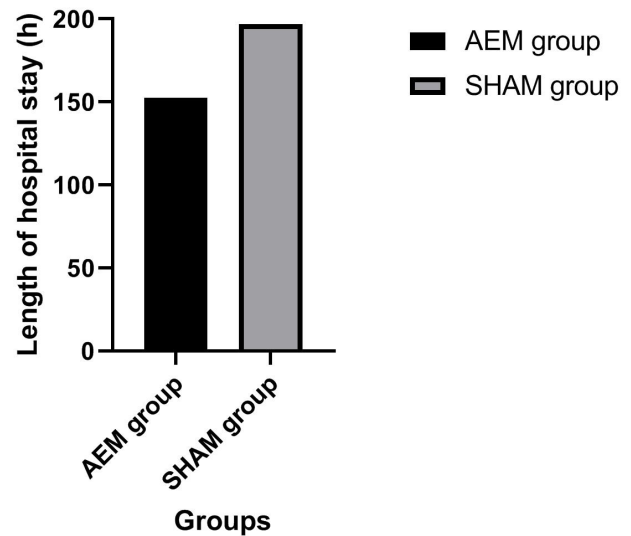


Figure 2. Length of hospital stay in ACE group and SHAM group ( $P < 0.05$ ).

ACE before surgery, and the SHAM group, which received sham ACE.

**Surgery and anesthesia:** All patients underwent general anesthesia induced with 0.1 mg/kg midazolam, 1.0 µg/kg sufentanil, 0.35 mg/kg etomidate, and 0.6 mg/kg rocuronium. Then, endotracheal intubation was performed. Before surgery, all patients had bilateral transversus thoracis muscle plane block with 40 ml of 0.4% ropivacaine. Propofol combined with remifentanyl was used for anesthesia maintenance, and supplemental boluses of rocuronium were used based on the clinical need. The BIS was maintained between 45 and 55 during the operation. All patients in our study received continuous infusion of sufentanil for postoperative analgesia. If patients complained of additional pain (NRS score  $\geq 4$ ), 50 mg flurbiprofen axetil was injected for additional treatment, which was repeated depending on the patient.

**Randomization and blindness:** The enrolled patients undergoing cardiac surgery were randomly assigned to two groups by a biostatistician using computer-generated numbers, and the information was kept in sealed envelopes. An investigator opened the envelopes, and he was the only one who knew whether the enrolled patient had undergone placement of chromic catgut strands. Another skilled doctor completed ACE on the evening before surgery. Data collectors had no knowledge of the patients' treatments. The anesthesiologists, nurses, enrolled patients, surgeons, and other investigators were blinded to the experimental grouping.

**Acupoint catgut embedding protocol:** The following acupuncture points were used for treatment: Shuifen (Conceptive vessel-9, REN-9), bilateral Zusanli (Stomach-36, ST-36), bilateral Shuidao (Stomach-28, ST-28), bilateral Siman (Kidney-14, KID-14), and Qihai (Conceptive vessel-6, REN-6). In the ACE group, catgut was embedded to a depth of 1.0 cm in both feet and to a depth of 1.5 cm

Table 2. Measures of Blood Markers and Insulin Resistance

|                   | Baseline     | 1 day after surgery | 3 days after surgery | 5 days after surgery | 7 days after surgery |
|-------------------|--------------|---------------------|----------------------|----------------------|----------------------|
| Insulin (units/l) |              |                     |                      |                      |                      |
| SHAM group        | 12.45 ± 1.59 | 17.84 ± 3.24*       | 16.72 ± 2.96*        | 15.59 ± 2.72*        | 15.37 ± 1.97*        |
| ACE group         | 12.32 ± 1.69 | 14.28 ± 2.17*       | 14.12 ± 2.07*        | 13.14 ± 1.52*        | 12.98 ± 1.47*        |
| Glucose (mmol/l)  |              |                     |                      |                      |                      |
| SHAM group        | 6.42 ± 2.35  | 7.55 ± 3.32*        | 7.25 ± 2.94*         | 7.12 ± 2.78*         | 6.85 ± 2.28*         |
| ACE group         | 6.37 ± 2.28  | 6.94 ± 2.82*        | 6.79 ± 2.38*         | 6.63 ± 2.28*         | 6.47 ± 2.18*         |
| HOMA-IR           |              |                     |                      |                      |                      |
| SHAM group        | 2.83 ± 0.64  | 4.89 ± 0.82*        | 4.67 ± 0.72*         | 4.46 ± 0.68*         | 4.37 ± 0.65*         |
| ACE group         | 2.73 ± 0.54  | 3.86 ± 0.68*        | 3.76 ± 0.76*         | 3.54 ± 0.57*         | 3.49 ± 0.49*         |
| IL-6 (pg/ml)      |              |                     |                      |                      |                      |
| SHAM group        | 62.25 ± 8.68 | 92.21 ± 9.52*       | 96.32 ± 8.98*        | 93.45 ± 7.69*        | 89.56 ± 7.89*        |
| ACE group         | 63.16 ± 7.46 | 82.42 ± 8.18*       | 85.65 ± 7.89*        | 83.35 ± 7.65*        | 80.13 ± 6.98*        |
| IL-8 (pg/ml)      |              |                     |                      |                      |                      |
| SHAM group        | 32.26 ± 6.32 | 45.32 ± 5.65*       | 48.34 ± 4.98*        | 46.23 ± 3.86*        | 43.31 ± 3.68*        |
| ACE group         | 31.61 ± 5.89 | 36.57 ± 4.18*       | 37.41 ± 4.28*        | 36.21 ± 3.98*        | 34.23 ± 3.54*        |

\* $P < 0.05$ ;  $P < 0.05$  considered statistically significant

in the abdomen using a syringe needle. When the patient felt sourness, the syringe needle was withdrawn, and the catgut was left inside the tissue. For the SHAM group, the same embedding acupoints were punctured with the syringe needle without the placement of chromic catgut strands. Acupuncture required retaining the needle in the acupoints achieve “qi,” while in the SHAM group in our trial, the acupoints were only punctured, without activating “qi.” Therefore, we called this group the SHAM group instead of the acupuncture group to avoid confusion.

**Clinical and biochemical parameters:** The primary outcome of our trial was insulin resistance assessed 1, 3, 5, and 7 days after surgery. Insulin resistance was assessed by the homeostasis model assessment, that is, HOMA-IR = blood glucose (mmol/l) x blood insulin (munits/ml)/22.5. Secondary outcomes included insulin, glucose, inflammatory cytokines interleukin (IL) IL-6, IL-8, time to extubation, incidence of infections, time to first feces, acute kidney injury, incidence of postoperative nausea and vomiting (PONV), length of stay in the ICU, length of hospital stay, and other clinical parameters. All blood was immediately centrifuged at 1500 rpm for 20 minutes to separate the plasma. Then it was frozen at  $-70^{\circ}\text{C}$  for subsequent analysis.

**Statistical analysis:** The calculation of the sample size in our trial was based on a pilot study, which included 18 patients in each group according to the primary outcome, insulin resistance at 24 hours after surgery. An enrollment of 46 patients per group was required with a type I error of  $\alpha = 0.05$ , a type II error of  $\beta = 0.2$  and a power of 90%. We finally included 20% more patients for analysis to compensate for possible dropout in our trial ( $N = 50$  in each group).

All data were analyzed using SAS software (version 9.1.3, North Carolina, USA). The continuous data were expressed as the mean and standard deviation, whereas the qualitative data were expressed as the frequency and percentage. The skewness and Kurtosis tests were used to test the normal distribution of continuous data. Student's *t* test was used to assess the intergroup differences with normal distribution, whereas the Wilcoxon Mann-Whitney test was used to assess the differences in the non-normally distributed data. The Chi-square or Fisher's exact test were used to analyze categorical data. Biochemical data were evaluated by ANOVA for repeated measurements. A probability value of less than 5% was considered significant.

## RESULTS

One hundred patients were screened for our study. Eight patients were excluded for the following reasons: cancellation of elective surgery after the embedding protocol (three), refused blood collection after surgery (three) and underwent redo surgery (two); the data from 92 patients were finally analyzed ( $N = 46$  per group) (Figure 1). All enrolled patients tolerated ACE well and had no adverse reactions. There were no differences in the baseline characteristics of the ACE and SHAM groups (Table 1).

There were no significant differences in the levels of insulin, glucose, IL-6, IL-8, or HOMA-IR between the ACE and SHAM groups at baseline. The ACE group had a lower blood glucose level than the SHAM group one week after the operation (Table 2). Postoperatively, the insulin, IL-6, IL-8, and HOMA-IR levels

Table 3. Intra- and Postoperative Clinical Outcomes

|                                      | AEM group<br>(N = 46) | SHAM group<br>(N = 46) | P    |
|--------------------------------------|-----------------------|------------------------|------|
| Time to extubation                   | 7.8 ± 4.5             | 8.3 ± 5.2              | .57  |
| Incidence of infections (%)          | 2(4.3)                | 5(10.9)                | <.01 |
| Time to first feces                  | 35.7 ± 5.9            | 38.2 ± 7.1             | .64  |
| Incidence of acute kidney injury (%) | 5(10.9)               | 6(13.1)                | .57  |
| Length of stay in the ICU            | 22.1 ± 4.7            | 24.3 ± 5.7             | .84  |
| Incidence of PONV (%)                | 4(8.7)                | 10(21.7)               | <.01 |
| Length of hospital stay (h)          | 152.5 ± 39.4          | 196.7 ± 42.5           | <.01 |
| Time to drain removal (h)            | 22.1 ± 4.7            | 29.3 ± 6.8             | .03  |

P < .05 considered statistically significant

increased to a higher degree in the SHAM group than in the ACE group 1, 3, 5, and 7 days after surgery (Table 2).

The incidence of infection, incidence of PONV, time to drain removal and length of hospital stay were significantly lower in the ACE group than in the SHAM group (Table 3). There were no significant differences between groups, in terms of the time to extubation, time to first feces, incidence of acute kidney injury and length of stay in the ICU (Table 3).

## DISCUSSION

This study demonstrates that ACE in REN-9, ST-36, ST-28, KID-14, and REN-6 before cardiac surgery reduces postoperative insulin resistance and systemic inflammation and maintains steady blood sugar levels, and these results might provide a basis for reducing the incidence of infection, incidence of PONV, time to drain removal and length of hospital stay after surgery.

The severe trauma due to sawing the sternum, cardiopulmonary bypass, and diabetes would have resulted in severe postoperative insulin resistance, systemic inflammation, and hyperglycemia in the patients in our study without any treatment. In cardiac patients, postoperative hyperglycemia and insulin resistance are associated with poor outcomes, including increased morbidity and mortality, increased frequency of infection, delayed healing and prolonged duration of hospital stay [Floh 2020; Zhang 2019]. However, other investigators have recognized that ACE can produce significant reductions in glucose, insulin, and HOMA-IR levels without adverse side effects. Similarly, Yan et al showed that ACE allowed control of insulin resistance in obese rats. In the present study, we also found that ACE efficiently controlled hyperglycemia and insulin resistance in elective open cardiac surgery. In addition, this was the first randomized controlled clinical study to apply ACE in cardiac surgery patients. Perioperative insulin resistance is most severe on the first postoperative day and can last up to one week [Svanfeldt 2007]. ACE is an improved form of classic acupuncture and compared with other types of

acupuncture, it has the advantages of longer lasting stimulation, a lower expense and a shorter time without additional biological effects [Liao 2014]. Therefore, in our study, ACE exerted a sufficiently powerful role in alleviating insulin resistance and hyperglycemia for seven days.

A reduction in insulin resistance is associated with a decreased release of inflammatory mediators, and it can diminish postoperative mortality and morbidity [Sato 2010]. Vlasselaers et al found that insulin had the ability to attenuate systemic inflammation and improve organ function as it possessed anti-inflammatory properties [Vlasselaers 2010]. Therefore, the difference in postoperative insulin resistance was the main reason for the difference in IL-6 and IL-10 levels between the two groups in our study. Reduced postoperative insulin resistance and a reduced inflammatory response might have been the basis for the good clinical outcome in the ACE group.

Ouattara et al showed that diabetic patients undergoing elective cardiac surgery without controlling postoperative hyperglycemia were associated with a seven-fold higher risk of infection [Ouattara 2005]. Similarly, a study in 409 enrolled patients concluded that postoperative hyperglycemia was an independent risk factor for an increasing incidence of infection [Gandhi 2005]. The results of our trial indicated that ACE could effectively maintain stable blood sugar levels in cardiac patients and reduce the incidence of incision infection. Furthermore, the time to drain removal decreased after surgery in our study.

PONV can cause electrolyte imbalance, dehydration, pulmonary aspiration, and delayed hospital discharge [Kovac 2013; Bisgaard 2004], representing the most significant complications after surgery. A systematic review demonstrated that acupoint therapy is an effective and safe intervention for PONV [Yang 2019]. ACE reduced the incidence of PONV in diabetic patients undergoing cardiac surgery and had a significantly positive impact on the recovery and quality of life of patients. In addition, ACE was an inexpensive and noninvasive method to treat PONV in surgery patients.

Finally, reducing perioperative insulin resistance and reducing the inflammatory response are major therapeutic goals for decreasing the length of hospital stay after surgery [Nygre 2001]. Other reasons for the reduced length of hospital stay include the maintenance of stable blood sugar levels, reduction of postoperative incision infection rates and incidence of PONV, and earlier time to drain removal after surgery.

Nonetheless, this study still contains a few limitations. First, although there were no adverse effects of ACE in our experiment, it was still hard to evaluate the safety of ACE because of the lack of data from primary studies. Second, we did not know whether sham ACE with needle stimulation had an influence on patients undergoing elective cardiac surgery. Third, there was no further follow up to observe the future effects of ACE in cardiac patients.

## CONCLUSION

This study showed that the use of ACE in diabetic patients undergoing open cardiac surgery attenuated postoperative



insulin resistance and systemic inflammation. It shortened the length of hospital stay by reducing the incidence of infection, incidence of PONV, and time to drain removal.

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