

Does long-term high-altitude exposure reduce myocardial injury and incidence of acute kidney injury following cardiac surgery? A propensity score matched study

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Research

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Abstract

Objective

Chronic high-altitude exposure has been shown to reduce ischemia-reperfusion injury in animal experiments. The objective was to evaluate the clinical protective effect of long-term high-altitude hypoxic exposure for patients undergoing cardiac surgery with cardiopulmonary bypass.

Methods

In this retrospective cohort study, data from patients who underwent cardiac procedures between January 2013 and December 2019 at a single center was collected. Patients were divided into highlander group (> 2500 m) and lowlander group (< 1500 m) according to the altitude of their residence. A propensity-score-matched analysis was performed to estimate the association of long-term high-altitude exposure and cardiac surgery outcomes.

Results

In a total of 2085 patients, 128 highlander patients were matched to 248 lowlander patients. The levels of CK-MB and hs-TnI upon arrival at the intensive care unit were lower in the highlander group compared to the lowlander group [70.6 U/L (56.0, 92.6) vs 85.0 U/L (68.5, 113.5), $P < 0.001$; 6.1 ng/mL (3.3, 11.2) vs 7.9 ng/mL (3.6, 14.1), $P = 0.011$, respectively]. The highlander group also had a lower incidence of acute kidney injury (13.3% vs 21.8%, $P = 0.046$). The in-hospital mortality in the highlander group was lower than in the lowlander group without statistical significance (0.8% vs 4.0%, $P = 0.107$).

Conclusions

Long-term high-altitude exposure was associated with less myocardial injury and a lower incidence of acute kidney injury after cardiac surgery.

Background

Postoperative organ injuries after cardiac surgery are associated with significant mortality and morbidity. Most of them are attributed to ischemia/reperfusion (I/R) injury. Numerous preventive strategies reducing I/R injury, such as ischemic or hypoxic preconditioning and postconditioning, are limited and unfeasible to apply in clinical practice [1]. Remote ischemia preconditioning (RIPC) has been shown to be protective in animal studies and feasible in clinical practice, however, the results of recent clinical studies have been controversial [2–5]. Therefore, the protective effect of chronic ischemic and hypoxic preconditioning has garnered much attention [6].

The high-altitude residents live in chronic and potent hypoxic environment. The cardioprotective effect of chronic high-altitude hypoxia against various manifestations of acute I/R injury has been confirmed for a long time [7]. Animal experiments have shown that adaptation to chronic hypoxia can increase the tolerance to myocardial infarct, contractile dysfunction and ventricular arrhythmias [8, 9]. Coincidentally, the mechanisms of protection conferred by long-term high-altitude hypoxia (long-lasting effects) and preconditioning (short-lived preconditioning) seem to share the similar signaling pathways, including hypoxia-inducible factor-1 (HIF-1) and nuclear factor E2-related factor (2Nrf2) [6, 10]. The facts that make them different are that the myocardial protective effect of long-term high-altitude hypoxia lasted 5 weeks longer than that of preconditioning [11] and long-term high-altitude hypoxia also affects the expression of some proteins associated with maintaining oxygen homeostasis [12].

Many epidemiological surveys showed that patients with coronary heart disease who have been exposed to high altitudes for a long time had better survival than those in plain areas [13–15]. However, it is unknown if similar protective effects exist for patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) living in high-altitude areas. Therefore, we designed this retrospective cohort study to evaluate the impact of long-term high-altitude exposure on outcomes after cardiac surgery.

Materials And Methods

Study population

3028 consecutive patients who underwent cardiac procedures at the Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, China, between January 1, 2014 and December 31, 2019, were retrospectively reviewed. Previous studies have demonstrated that significant cardiovascular changes especially in pulmonary vascular system occur at altitudes above 2500 meters [16]. Moderate altitude and high altitude were described as 1500–2500 meters and > 2500 meters, respectively. For this reason, altitudes of 1500 and 2500 meters were chosen as cutoffs. Using the electronic Google satellite map to search the altitude of their residence, patients born and permanently living below 1500 meters and had not lived at high-altitudes for > 2 weeks are considered as lowlanders (n = 1950), while those who were born and permanently live above 2500 meters are considered as highlanders (n = 135).

Exclusion criteria included: (1) patients born in low-altitude areas but living in high-altitude areas after adulthood; (2) patients who reside between 1500 meters and 2500 meters above sea level; (3) incomplete electronic records (including data used for propensity score matching, primary and secondary end points); (4) pregnancy; (5) emergency; (6) beating heart surgery.

A total of 2085 patients were enrolled in this study (Fig. 1). Detailed demographic information and surgical procedures, including complications and intensive care unit (ICU) data, were collected from the electronic medical record system.

Outcome Assessment And Definition Of Postoperative Complications

Outcome assessment and definition of postoperative complications

The primary outcomes include myocardial injury assessed by postoperative creatine kinase (CK)-MB and high-sensitivity cardiac Troponin I (hs-TnI) levels, as well as the incidence of acute kidney injury (AKI) assessed by KDIGO criteria [17]. Other outcomes such as requirement of intra-aortic balloon pump (IABP) support, new on-set stroke, in-hospital mortality, duration of mechanical ventilation, length of stay in ICU, and in-hospital length of stay were also assessed. Myocardial injury was assessed by the levels of CK-MB and hs-TnI upon arrival at the ICU. AKI was defined according to KDIGO 2012 CKD Guideline as an increase in serum creatinine of ≥ 0.3 mg/dl (≥ 26.5 μ M) within 48 h and an increase in serum creatinine of ≥ 1.5 times baseline known or presumed to have occurred within the prior 7 days [17]. New on-set stroke in this study was defined as a patient who had been diagnosed by neurology or ICU doctors according to the patient's physical signs and brain computed tomography (CT) scan to ensure the accuracy of diagnosis. Duration of mechanical ventilation was calculated from the time of extubation in the ICU and the time of arrival at the ICU, and additional duration of mechanical ventilation if there was a record of re-intubation.

Statistical analysis

The data were analyzed with a SPSS 23.0 software package. Continuous data were expressed as mean \pm standard deviation or median (25% percentile, 75% percentile), and compared with an unpaired *t*-test and Mann–Whitney *U* test, respectively. Categorical data were shown as frequency or percentages and compared with the χ^2 test or Fisher's exact test between the two groups. $P < 0.05$ was declared significantly.

Propensity Score Matching

In order to reduce the possibility of baseline and surgical covariate imbalance, propensity score matching was employed. Each highlander was matched to two lowlanders based on their propensity score, using the greedy matching protocol, and the fixed caliper width is 0.020. Replacement was unacceptable in the matching. We used the standardized differences of the covariate means and proportions to assess the balance in the pairing after matching. They achieve an acceptable balance, absolute standardized differences in all baseline characteristics were $< 10\%$. Adjusted baseline and surgical covariates were age, sex, body mass index (BMI), creatinine, left ventricular ejection fraction (LVEF), history of hypertension, history of diabetes, atrial fibrillation (AF), stroke, myocardial infarction (MI), heart failure (HF), peripheral arterial disease, chronic obstructive pulmonary disease (COPD), history of surgery, type of surgery, and cardiopulmonary bypass duration (Table 1).

Table 1
Baseline characteristics of the study patients before and after propensity score matching.

	Entire cohort		P value	Propensity matched cohort		
	Lowlander group (< 1500 m)	Highlander group (> 2500 m)		Lowlander group (< 1500 m)	Highlander group (> 2500 m)	P value
N	1950	135		248	128	
Demographics						
Age, y	47.1 ± 16.4	36.4 ± 18.6	< 0.001	38.1 ± 18.5	37.1 ± 18.2	0.638
Sex			0.078			0.715
Female, n (%)	1120 (57.4)	88 (65.2)		160 (64.5)	85 (66.4)	
Male, n (%)	830 (42.6)	47 (34.8)		88 (35.5)	43 (33.6)	
BMI, kg/m ²	22.2 ± 3.7	21.7 ± 4.8	0.170	21.7 ± 4.3	21.5 ± 4.6	0.693
Creatinine, µM	68.8 ± 37.2	57.6 ± 18.6	0.001	58.8 ± 20.7	58.4 ± 18.3	0.861
LVEF	0.63 ± 0.10	0.64 ± 0.08	0.073	0.65 ± 0.09	0.64 ± 0.08	0.638
History variables, n (%)						
Hypertension	291 (14.9)	12 (8.9)	0.054	17 (6.9)	12 (9.4)	0.385
Diabetes mellitus	108 (5.5)	2 (1.5)	0.041	4 (1.6)	2 (1.6)	1.000
History of AF	762 (39.1)	37 (27.4)	0.007	71 (28.6)	36 (28.1)	0.918
Prior stroke	170 (8.7)	5 (3.7)	0.042	12 (4.8)	5 (3.9)	0.680
Previous MI	17 (0.9)	0 (0.0)	0.621	0 (0.0)	0 (0.0)	-
HF	87 (4.5)	4 (3.0)	0.410	12 (4.8)	4 (3.1)	0.435
Peripheral arterial disease	23 (1.2)	0 (0.0)	0.396	0 (0.0)	0 (0.0)	-
COPD	47 (2.4)	2 (1.5)	0.767	2 (0.8)	2 (1.6)	0.608
Prior surgery	48 (2.4)	1 (0.7)	0.369	1 (0.4)	1 (0.8)	1.000
Data are presented as the mean (SD) or number (%). Abbreviations: LVEF = left ventricular ejection fraction. AF = atrial fibrillation. MI = myocardial infarction. HF = heart failure. COPD = chronic obstructive pulmonary disease.						

Results

Baseline characteristics and surgical data

A total of 2085 patients who underwent cardiac surgery with CPB were included for initial analysis, with 42.1% male patients and 57.9% female patients. Of all the patients, 14.5% had hypertension, and 5.3% had diabetes mellitus. All the baseline characteristics used for propensity score matching are shown in Table 1. A majority of the patients (65.0%) underwent valve surgeries. The surgical data used for propensity score matching are shown in Table 2. Based on the propensity score, 128 highlanders were 1:2 matched to 248 lowlanders (eight highlanders only matched to one lowlander). There were no statistically significant differences in baseline characteristics and surgical data after matching.

Table 2
Surgical characteristics of study patients before and after propensity score matching.

	Entire cohort			Propensity matched cohort		
	Lowlander group	Highlander group	P value	Lowlander group	Highlander group	P value
	(< 1500 m)	(> 2500 m)		(< 1500 m)	(> 2500 m)	
N	1950	135		248	128	
CABG (any, <i>n</i> (%))	94 (4.8)	2 (1.5)	0.073	3 (1.2)	1 (0.8)	1.000
Aortic surgery (any, <i>n</i> (%))	136 (7.0)	9 (6.7)	0.892	11 (4.4)	9 (7.0)	0.288
Valve surgery (any, <i>n</i> (%))	1268 (65.0)	63 (46.7)	<0.001	120 (48.4)	62 (48.4)	0.993
CHD (any, <i>n</i> (%))	381 (19.5)	55 (40.7)	<0.001	103 (41.5)	51 (39.8)	0.752
Myxoma surgery (any, <i>n</i> (%))	65 (3.3)	5 (3.7)	0.803	11 (4.4)	5 (3.9)	0.810
Constrictive pericarditis surgery (any, <i>n</i> (%))	6 (0.3)	1 (0.7)	0.375	0 (0.0)	0 (0.0)	-
CPB duration, min	131.3 ± 57.0	111.1 ± 46.3	< 0.001	114.7 ± 53.8	111.8 ± 46.3	0.605

Data are presented as the mean (SD) or number (%). Abbreviations: CABG = coronary artery bypass grafting. CHD = congenital heart disease. CPB = cardiopulmonary bypass.

Patient Outcomes

The in-hospital mortality in the lowlander group is 4 times higher than that in the highlander group, however, the difference had no statistical significance [4.0% (10/248) vs 0.8% (1/128), $P > 0.05$] (Table 3).

The matched cohort analysis revealed that CK-MB and hs-Tnl levels increased more in the lowlander group on arrival at the ICU [70.6 U/L (56.0, 92.6) vs 85.0 U/L (68.5, 113.5), $P < 0.001$; 6.1 ng/mL (3.3,11.2) vs 7.9 ng/mL (3.6, 14.1), $P < 0.05$, respectively] (Table 3). However, the incidences of IABP support after surgery, as well as new on-set stroke, were similar between the two matched groups. The highlander group had a lower rate of AKI (13.3% vs 21.8%, $P < 0.05$) (Table 3). There was no significant difference in the duration of mechanical ventilation, length of stay in ICU, and in-hospital length of stay ($P > 0.05$) (Table 3).

Table 3

Comparison of outcomes between the lowlander group and the highlander group (after propensity score matching).

Postoperative indicators	Lowlander group (<i>n</i> = 248)	Highlander group (<i>n</i> = 128)	<i>P</i> value
In-hospital death, <i>n</i> (%)	10 (4.0)	1 (0.8)	0.107
CK-MB, U/L	85.0 (68.5, 113.5)	70.6 (56.0, 92.6)	<0.001
hs-Tnl, ng/mL	7.9 (3.6, 14.1)	6.1 (3.3,11.2)	0.011
IABP support	1 (0.4)	1 (0.8)	1.000
New on-set stroke, <i>n</i> (%)	3 (1.2)	2 (1.6)	1.000
Acute kidney injury, <i>n</i> (%)	54 (21.8)	17 (13.3)	0.046
Mechanical ventilation time, h	10.8 (5.1, 19.3)	8.9 (5.0, 18.7)	0.317
ICU length of stay, h	24.6 (20.8, 62.6)	26.1 (20.7, 67.9)	0.929
In-hospital length of stay, days	11.4 (8.0, 16.6)	11.9 (8.8, 17.5)	0.621
Data are presented as the mean (SD), median (IQR) or number (%). CK-MB and hs-Tnl were tested when patients entered the ICU. The reference ranges of CK-MB and hs-Tnl were 0–25 U/L and 0–0.03 ng/mL, respectively. Abbreviations: CK-MB = creatine kinase. hs-Tnl = high-sensitivity cardiac Troponin I. IABP = intra-aortic balloon pump. ICU = intensive care unit.			

Discussion

Main findings

As far as we know, this is a study with the largest sample size to date to investigate the impact of long-term high-altitude exposure on outcomes of cardiac surgery under CPB. In the present study, we found that long-term high-altitude exposure before cardiac surgery could reduce the myocardial injury, e.g., the levels of CK-MB and hs-Tnl after surgery compared to the lowlanders. Meanwhile, patients in the highlander group had a statistically significant lower risk of AKI than those in the lowlander group. Moreover, long-term high-altitude exposure was associated with lower mortality after cardiac surgery despite no statistical significance. These clinical findings are consistent with previous studies where long-

term high-altitude hypoxia has cardioprotective effect in animal models [8]. In addition, our study also showed that long-term high-altitude exposure might be effective for renal protection and decreasing the mortality after cardiac surgery.

Long-term High-altitude Exposure And Myocardial Injury

The cardioprotective effect of long-term high-altitude hypoxia against acute I/R injury has been known for a long time in animals. High-altitude hypoxia increased the tolerance of animal hearts to I/R injury determined as reduction of infarct size, and decreased the incidence and severity of arrhythmias [10]. It is necessary to verify that the cardioprotective effect of high-altitude hypoxic adaption remains in some clinical settings. In this retrospective study, myocardial injury was assessed by CK-MB and hs-TnI levels on arrival at the ICU and requirement of IABP after cardiac surgery. Except for IABP, the levels of CK-MB and hs-TnI were significantly different between the two matched groups, indicating that the cardioprotective effect of long-term high-altitude hypoxia also works in I/R injury induced during CPB. This is consistent with previous experimental results [18], although previous experiments mainly studied ischemic heart disease such as coronary heart disease [19]. Furthermore, studies have indicated that Tibetans, the main component of the highlander group, who live at high altitude for generations are more tolerant to hypoxia, and they have fewer deleterious changes such as elevated hemoglobin and pulmonary hypertension [20]. To maintain heart function in chronic hypoxia environments, high-altitude natives conduct a metabolic adaptation that leads to an altered substrate preference, meaning their myocardial metabolism switches toward the use of glucose as the substrate when oxygen levels are diminished [21]. This change in metabolic substrate can reduce the defects in heart efficiency and function that occur during myocardial I/R.

Long-term High-altitude Exposure And Aki

Renal protection strategies such as ischemic/hypoxic preconditioning (mainly in rodents) have been published decades ago and their extraordinary effectiveness has raised the hope for powerful clinical tools to prevent acute kidney injury [22]. So far, translation to the clinical medicine has not been successful. Nevertheless, some clinical studies using RIPC strategies have drawn positive conclusions [23, 24]. As described earlier in this study, the mechanism of long-term high-altitude hypoxia is similar to that of ischemia preconditioning [10]. This may be the reason why patients in the highlander group had a significantly lower risk of AKI than those in the lowlander group. It is worth noting that the protective effect of long-term high-altitude hypoxia may weaken or even disappear after reaching the plain area and breaking away from the hypobaric hypoxia environment. This might explain the diminished difference in renal replacement therapy between the two groups at long term follow up.

Mechanisms Of Organ-protective Effects Induced By Long-term High-altitude Exposure

Although the protective effect of chronic high-altitude hypoxia has been verified by many experiments, its mechanism needs further study. In high-altitude hypoxia environment, sympathetic system is activated [25]. Catecholamines contribute to the induction of cardioprotection by long-term high-altitude hypoxia. Studies have shown that the cardioprotective effect in a dog model of intermittent hypoxia can be completely prevented by administration of the 1-adrenoceptor antagonist metoprolol before each hypoxic session. Reactive oxygen species (ROS) also plays a very important role. Milano et al [26] suggested that repeated reoxygenation could produce better myocardial protection than chronic hypoxia. However, the duration of hypoxia exposure in native highlanders is much longer than that of repeated reoxygenation or chronic hypoxia administration. The intensity of hypoxia exposure might produce a sufficient mechanism of myocardial or other organ protection in highlanders. Furthermore, the endogenous production of nitric oxide (NO) and its therapeutic effects have been confirmed by a number of studies in I/R [27]. Application of NO or NO donors before heart ischemia can reduce the severity of myocardial IR injury, thereby reducing the infarct size and endothelial dysfunction. Coincidentally, levels of NO were elevated in the circulation of Tibetans to increase the oxygen supply to cells when united with increased ventilation [20]. Nevertheless, the mechanisms of organ-protective effects induced by long-term high-altitude exposure need to be comprehensively investigated in the future.

Limitations

The present study has several limitations. First, the sample size of high-altitude patients is limited because of the relatively few populations in high altitude areas. Furthermore, as a retrospective study, some complications such as the occurrence of arrhythmia, might be missing for data collection. Therefore, we chose the myocardial injury markers collected on arrival at the ICU to evaluate the myocardial injury. Since not every patient had follow up cardiac enzymes after ICU arrival, we were unable to collect longer follow up laboratory data. Finally, we identified the long-term high-altitude exposure with improved surgical outcome after cardiac surgery, however, we could not identify the exact mechanism behind this, and if this was due to hypoxia/ischemia preconditioning. Further study in human myocardial tissue samples may help us to understand the mechanism.

Conclusions

This study demonstrated that long-term high-altitude exposure was associated with lower levels of CK-MB and hs-TnI, and a lower risk of AKI after cardiac surgery, suggesting that long-term high-altitude exposure may be beneficial for reducing I/R organ injury after cardiac surgery with CPB.

Abbreviations

I/R ischemia/reperfusion

RIPC Remote ischemia preconditioning

HIF-1 hypoxia-inducible factor-1

2Nrf2 nuclear factor E2-related factor

CPB cardiopulmonary bypass

ICU intensive care unit

AKI acute kidney injury

CK creatine kinase

hs-Tnl high-sensitivity cardiac Troponin I

CT computed tomography

KDGIO Kidney Disease: Improving Global Outcomes

BMI body mass index

LVEF left ventricular ejection fraction

AF atrial fibrillation

MI myocardial infarction

HF heart failure

COPD chronic obstructive pulmonary disease

ROS Reactive oxygen species

NO nitric oxide

Declarations

Availability of data and materials

The datasets generated and/ or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical statement

This retrospective cohort study was conducted at the Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, China. The study was approved by the hospital Human Research

Ethics Committee in April 2020 (No. 2020–54), and the requirement for written informed consent was waived.

Consent for publication

Not applicable.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

Meng-xue Liu, Man Wang: Data curation, formal Analysis, writing – original draft

Jia Huang: Data curation, project administration

Zuojia Zeng, Keli Huang, Xinquan Liu: Data curation, follow-up

Xin-chuan Wei, Qian Lei: Conceptualization, funding acquisition, methodology, supervision, writing – review & editing

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Figures

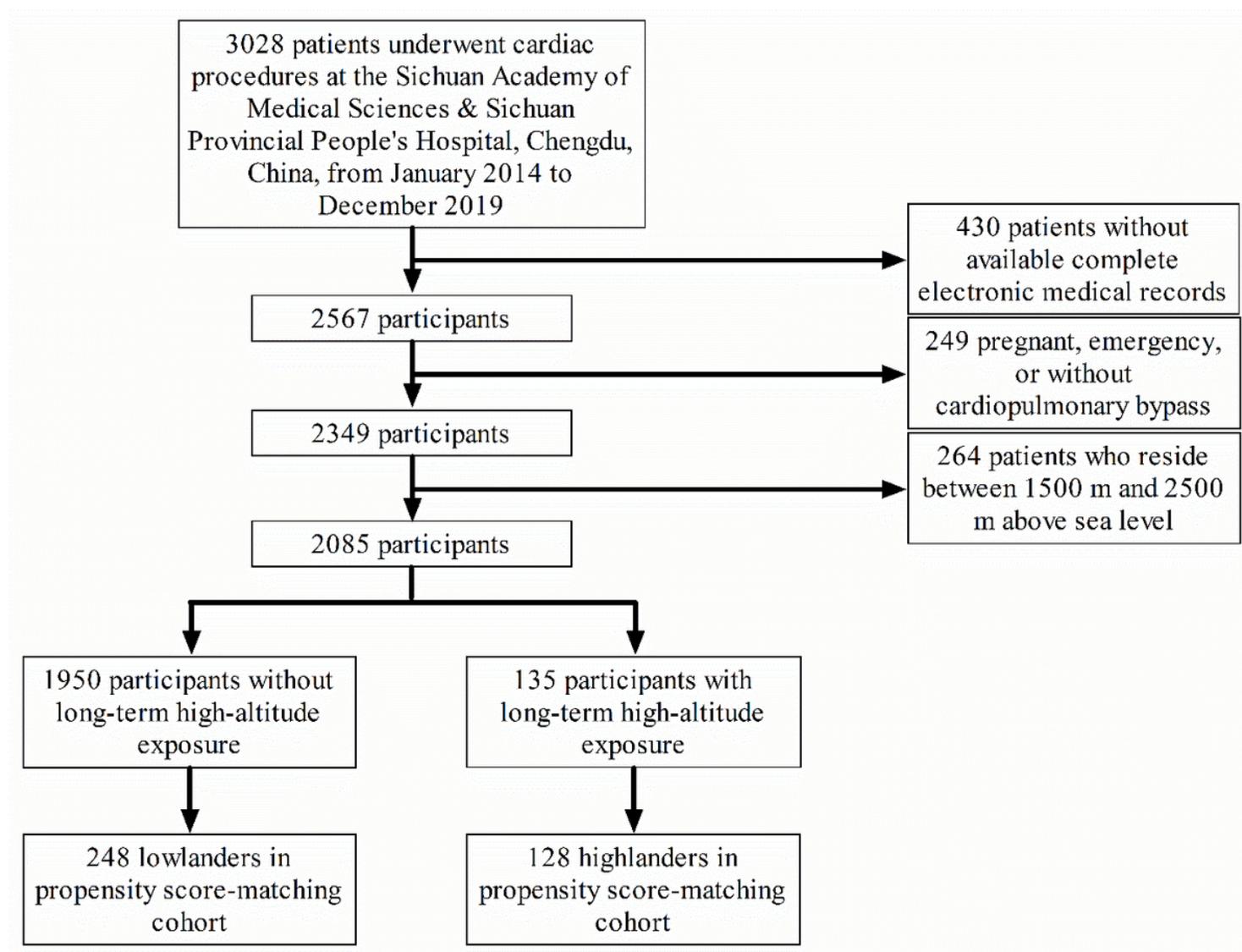


Figure 1

Study inclusion criteria.