Research Letter

Analysis of circulatory mitochondrial DNA level after cardiac surgery with cardiopulmonary bypass and potential prognostic implications

A B S T R A C T

Our research letter found that circulatory mtDNA level increased after the end of CPB and positive correlations between mtDNA and peak CRP level, peak BNP level, and peak PCT level, which revealed the prognostic role of perioperative circulatory mtDNA level in patients who underwent cardiopulmonary bypass.

© 2016 Cardiological Society of India. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Cardiopulmonary bypass (CPB) has been widely applied since 1950s, and there are still some indications of harmful effects of CPB.1 Mitochondrial DNA (mtDNA) fragments, referred as damage-associated molecular patterns, can lead to a series of molecular processes causing inflammatory responses in several diseases.2 In the present letter, we focused on clinic demonstrations of the perioperative circulatory mtDNA level in patients who underwent cardiac surgery with CPB.

46 consecutive patients were included in our study, who required surgical double valve replacement (aortic valve and mitral valve) from June 2014 to December 2014 at West China Hospital (Chengdu, China). Circulatory levels of mtDNA were measured by real-time PCR. Briefly, blood samples were collected at admission (T1), the end of CPB (T2), 6 h postoperation (T3), 12 h postoperation (T4), and 24 h postoperation (T5). The mtDNA copy numbers were quantified with 10-fold serial diluted standard curves. The forward primer 5′-CGAGCAGTAGCCCAAACAAT-3′ and reverse primer 5′-TGTGATAAGGGTGAGGGGT-3′ were used. The mtDNA levels were compared for well-known biomarkers, such as C-reactive protein (CRP), B-type natriuretic peptide (BNP), and procalcitonin (PCT). Informed consent was obtained from every patient. The study was conducted following Declaration of Helsinki and approved by the research committee in the Sichuan University.

Basic patient characteristics, surgery information, and laboratory data are shown in Table 1. All surgeries were performed successfully with no fatalities and all patients were discharged from the hospital. Four patients exhibited low output syndrome and two patients had renal failure after surgery. Circulatory mtDNA level was significantly higher from T2 to T5 than T1 (p < 0.05). These levels peaked at T4 (905 ± 191 copies/μL), at which point they were significantly correlated with peak CRP levels (r = 0.72, p < 0.01), peak BNP levels (r = 0.638, p < 0.01), and peak PCT levels (r = 0.588, p < 0.01) (Fig. 1).

It is well known that postoperative inflammatory responses are highly related to the prognosis of cardiac surgery. Accordingly, we inferred that mtDNA release after cardiac surgery may cause inflammatory responses and influence the prognosis of cardiac surgery. Furthermore, many studies have illustrated that concentrations of CRP, PCT, and BNP are associated with the magnitude of operative injuries.3 Analyses with peak levels of these known predictors, weak but significant correlations with circulatory mtDNA level at T4 were detected. The results of the present study suggest that mtDNA is a promising prognostic predictor of cardiac surgery with CPB. In fact, mtDNA is already considered as a marker for predicting oxidative stress in obstructive sleep apnea and mortality in intensive care patients, and our results suggest an additional prognostic application of mtDNA.4,5

In the present preliminary study, we found that, after cardiac surgery with CPB, the circulatory mtDNA level increased and bivariate correlation analyses demonstrated significant correlations between mtDNA level and peak levels of CRP, BNP, and PCT.

Table 1

| Characteristic                        | N = 46 |
|---------------------------------------|--------|
| Age (years)                           | 48.8 ± 10.3 |
| Women                                 | 26 (56.5%) |
| Hypertension                          | 30 (65.2%) |
| Diabetes                              | 5 (10.9%) |
| Current smoker                        | 11 (23.9%) |
| Surgery information                   |        |
| Aortic cross-clamping time (min)      | 119 ± 21 |
| CPB time (min)                        | 138 ± 18 |
| Laboratory data                       |        |
| Serum creatinine (μmol/L)             | 0.5 ± 0.2 |
| Total cholesterol (mg/dL)             | 178.2 ± 38.9 |
| Glucose (mg/dL)                       | 142.1 ± 40.2 |
| CRP (mg/L)                            | 3.5 ± 2.9 |
| BNP (pg/mL)                           | 89 ± 68 |
| PCT (pg/mL)                           | 239 ± 121 |
| mtDNA (copies/μL)                     | 223 ± 23 |

Variables are presented as mean ± SD or as numbers (%). CRP, C-reactive protein; BNP, B-type natriuretic peptide; PCT, procalcitonin; mtDNA, mitochondrial DNA.

http://dx.doi.org/10.1016/j.ihj.2016.04.014
0019-4832/© 2016 Cardiological Society of India. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/)
which characterized the potential prognostic value of circulatory mtDNA.

**Conflicts of interest**

The authors have none to declare.

**Acknowledgement**

This study was financially supported by the National Natural Science Foundation of China (Nos. 8150036, 81370413, 81500213).

**References**

1. Tsakiridis K, Mpakas A, Kesisis G, et al. Lung inflammatory response syndrome after cardiac operations and treatment of lornoxicam. J Thorac Dis. 2014;6(suppl 1):578–598.
2. Qin C-y, Gu J, Qian H, Shi Y-k, Meng W. Variation of perioperative mitochondrial DNA concentration after cardiopulmonary bypass. Chin J Clin Thorac Cardiovasc Surg. 2015;22:248–251.
3. Watt DG, Horgan PG, McMillan DC. Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: a systematic review. Surgery. 2015;157:362–380.
4. Nakamura K, Kyung SY, Rogers AJ, et al. Circulating mitochondrial DNA in patients in the ICU as a marker of mortality: derivation and validation. PLoS Med. 2013;10:e1001577.
5. Kim YS, Kwak JW, Lee KE, et al. Can mitochondrial dysfunction be a predictive factor for oxidative stress in patients with obstructive sleep apnea? Antioxid Redox Signal. 2014;21:1285–1288.

Fig. 1. (A) Variants of perioperative circulatory mtDNA level after cardiac surgery with CPB. *p < 0.05 vs. T1, #p < 0.05 vs. T4, N = 46. (B) Circulatory mtDNA level at T4 was significantly correlated with peak CRP level (r = 0.72, p < 0.01). (C) Circulatory mtDNA level at T4 was significantly correlated with peak BNP level (r = 0.638, p < 0.01). (D) Circulatory mtDNA level at T4 was significantly correlated with peak PCT level (r = 0.588, p < 0.01). (T1: at admission; T2: the end of CPB; T3: 6 h postoperation; T4: 12 h postoperation; T5: 24 h postoperation.)