International Journal of Cardiology 171 (2014) e65–e69

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

Cinacalcet ameliorates cardiac fibrosis in uremic hearts through suppression of endothelial-to-mesenchymal transition

Min Wu [a], Ri-Ning Tang [a,1], Hong Liu [a], Ming-Ming Pan [a], Lin-Li Lv [a], Jian-Dong Zhang [a,b], Steven D. Crowley [b], Bi-Cheng Liu [a,*]

[a] Institute of Nephrology, Zhongda Hospital, Southeast University School of Medicine, Nanjing City, China
[b] Division of Nephrology, Department of Medicine, Duke Medical Center and Durham VA Medical Center, Durham, NC, USA

ARTICLE INFO

Article history:
Received 2 September 2013
Accepted 30 November 2013
Available online 7 December 2013

Keywords:
Cardiac fibrosis
Uremia
Cinacalcet
Parathyroid hormone
Endothelial-to-mesenchymal transition

Cardiac fibrosis is a common feature in patients with chronic kidney disease (CKD). Increasing evidence has shown that elevated parathyroid hormone (PTH) is causally involved in cardiac fibrosis [1–4]. Cinacalcet (CINA), a calcimimetic agent, reduces PTH levels without increasing circulating levels of calcium and phosphorus [5,6]. Recent studies have shown that CINA treatment markedly attenuated myocardial fibrosis and vascular remodeling [6,7]. However, the underlying mechanisms of this action are still unknown. Endothelial-to-mesenchymal transition (EndMT) plays an important role in the development of cardiac fibrosis [8,9]. The purpose of this study was to investigate whether CINA ameliorated cardiac fibrosis in rats with uremia was mediated by suppression of EndMT.

Study protocols were approved by the Ethical Committee of Southeast University. The rat model of uremia and secondary hyperparathyroidism was established as previously described [10]. Briefly, 8-week-old male Wistar rats were randomly divided into three groups: the control group (CTL, n = 6), the uremia group (U, n = 8) and the CINA-treated uremia group (U + CINA, n = 8). Uremia was induced by feeding rats a 0.75% adenine diet for 4 weeks. After adenine withdrawal, all animals were maintained on a 1.03% phosphorus diet for next 8 weeks. At initiation of the adenine diet, rats in the U + CINA group were orally treated with CINA (Santa Cruz Biotechnology, USA) once daily (10 mg/kg) until the end of experiment. The effect of elevated PTH on EndMT was also studied in primary aortic endothelial cells (ECs).

It was demonstrated that the area of cardiac fibrosis in the U group was significantly increased compared to controls, and it was significantly attenuated by the administration of CINA (Fig. 1A–B). And CINA also inhibited the expression of the extracellular matrix elements type I collagen and fibronectin in uremic hearts (Fig. 1C–E). Furthermore, there was significant up-regulation of mesenchymal markers FSP1 and α-SMA, and down-regulation of the endothelial marker CD31, while CINA markedly abrogated expression of EndMT-associated markers in uremic hearts (Fig. 2). Compared with the U group, serum PTH concentrations were significantly lower in uremic rats treated with CINA (440.64 ± 43.25 *vs* 326.54 ± 47.86, $p < 0.05$). To further confirm the causal effect of elevated PTH on induction of EndMT, an *in vitro* experiment with primary aortic ECs was performed. The results showed that PTH incubation increased expression of FSP1 and α-SMA and decreased expression of CD31 at mRNA and protein levels in a concentration and time dependent manner ($p < 0.05$).

In conclusion, our data demonstrated that elevation of PTH induces EndMT and contributes to cardiac fibrosis in uremic rats, which could be prevented by CINA treatment. These results suggest that strategies aiming at lowering PTH levels might exert cardiac protective effects through an anti-EndMT mechanism.

Acknowledgment

These studies were supported by grants from the National Natural Science Foundation of China (81130010, 81370919) and the Natural Science Foundation of Jiangsu Province (BK2011603, BK2012751).

References

[1] Custódio MR, Koike MK, Neves KR, et al. Parathyroid hormone and phosphorus overload in uremia: impact on cardiovascular system. Nephrol Dial Transplant 2012;27:1437–45.
[2] Cha H, Jeong HJ, Jang SP, et al. Parathyroid hormone accelerates decompensation following left ventricular hypertrophy. Exp Mol Med 2010;42:61–8.
[3] Rutledge MR, Farah V, Adeboye AA, et al. Parathyroid hormone, a crucial mediator of pathologic cardiac remodeling in aldosteronism. Cardiovasc Drugs Ther 2013;27:161–70.
[4] Amann K, Ritz E, Wiest G, Klaus G, Mall G. A role of parathyroid hormone for the activation of cardiac fibroblasts in uremia. J Am Soc Nephrol 1994;4:1814–9.
[5] Charytan C, Coburn JW, Chonchol M, et al. Cinacalcet hydrochloride is an effective treatment for secondary hyperparathyroidism in patients with CKD not receiving dialysis. Am J Kidney Dis 2005;46:58–67.
[6] Choi SR, Lim JH, Kim MY, et al. Cinacalcet improves endothelial dysfunction and cardiac hypertrophy inpatients on hemodialysis with secondary hyperparathyroidism. Nephron Clin Pract 2013;122:1–8.

* Corresponding author at: Institute of Nephrology, Zhongda Hospital, Southeast University School of Medicine, Nanjing City, 210009, China.
E-mail address: liubc64@163.com (B.-C. Liu).
[1] Co-first author.

http://dx.doi.org/10.1016/j.ijcard.2013.11.105

[7] Jung S, Querfeld U, Müller D, et al. Submaximal suppression of parathyroid hormone ameliorates calcitriol-induced aortic calcification and remodeling and myocardial fibrosis in uremic rats. J Hypertens 2012;30:2182–91.
[8] Zeisberg EM, Tarnavski O, Zeisberg M, et al. Endothelial-to-mesenchymal transition contributes to cardiac fibrosis. Nat Med 2007;13:952–61.
[9] Tang RN, Lv LL, Zhang JD, et al. Effects of angiotensin II receptor blocker on myocardial endothelial-to-mesenchymal transition in diabetic rats. Int J Cardiol 2013;162:92–9.
[10] De Schutter TM, Behets GJ, Geryl H, et al. Effect of a magnesium-based phosphate binder on medial calcification in a rat model of uremia. Kidney Int 2013;83:1109–17.

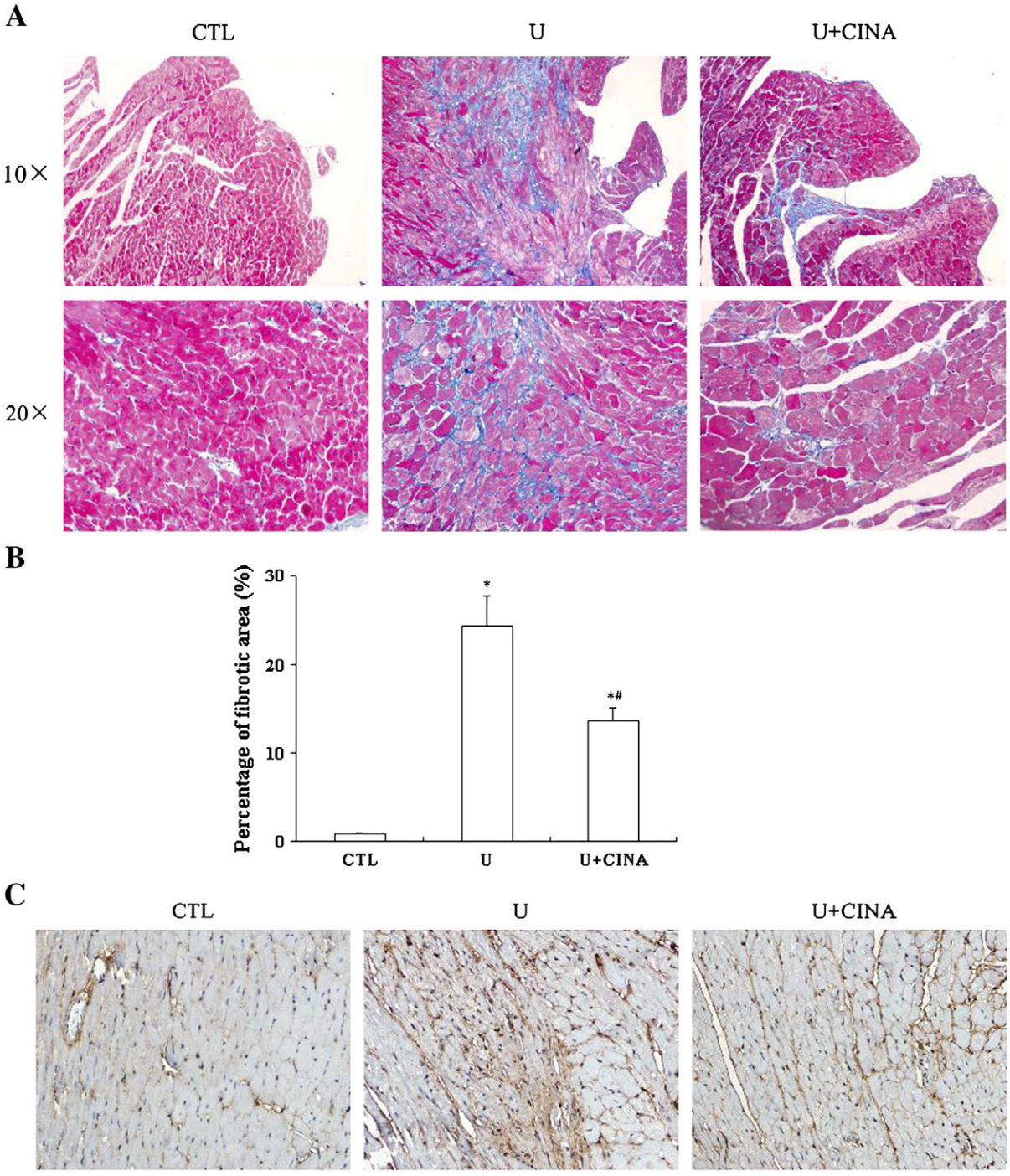

Fig. 1. Effect of CINA on fibrotic lesions in uremic hearts. (A) Cardiac fibrosis was assessed by Masson's trichrome staining. Images with different magnifications are shown. (B) Quantitative determination of cardiac fibrosis in the different groups. (C) Representative micrographs showing cardiac expression of type I collagen in the different groups of rats (original magnification is ×200). (D–E) Western blot analyses show the expression of type I collagen (D) and fibronectin (E). The data are expressed as the means ± SDs (n = 6 for each group). $^{*}P < 0.05$ *vs* the CTL group; $^{\#}P < 0.05$ *vs* the U group.