Original Article

Myocardial protection of propofol on apoptosis induced by anthracycline by PI3K/AKT/Bcl-2 pathway in rats

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Background: The release of proinflammatory cytokines is inhibited by propofol, which could reduce oxidative stress and suggests that propofol could ameliorate the adverse effects of anthracyclines in myocardial cells as a promising cardioprotective agent. The aim of the study was to evaluate the protective effects of propofol on phosphatidylinositol 3 kinase/protein kinase B/B cell lymphoma 2 (PI3K/AKT/Bcl-2) pathway in cardiomyocyte apoptosis induced by doxorubicin [adriamycin (ADM)] of rat cardiomyocytes *in vivo*.

Methods: The 40 F344 female rats were randomly divided into 4 groups (n=10): treatment control, ADM, Propofol (Prop) and ADM + Prop group. Blood samples were taken as baseline, before the 4th administration of the agents and before humane death. The serum levels of malondialdehyde (MDA), an oxidant factor, were detected by the thiobarbituric acid method. Superoxide dismutase (SOD) levels were analyzed by xanthine oxidase, and those of cardiac troponin I (cTnI), atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) were analyzed by enzyme linked immunosorbent assay (ELISA). Apoptosis of cardiac myocytes was measured by flow cytometry. The expression levels of PI3K-110α and pAKT-Ser473 and Bcl-2 proteins in rat heart tissue were detected by western blot.

Results: Apoptosis induced by ADM was significantly reduced by propofol. Compared with the ADM group, the serum levels of MDA, cTnI and BNP in the ADM + Prop group were significantly downregulated. In addition, the PI3K-110α and pAKT-Ser473 expressions in the ADM group were significantly higher than those in the ADM + Prop group, and the increases in Bcl-2 expression in the ADM + Prop group was statistically significant compared with the ADM group.

Conclusions: We identified that the PI3K/AKT/Bcl-2 axis is involved in the regulation of cardiomyocyte apoptosis induced by ADM *in vivo*. In addition, our results elucidated that propofol had a protective role in cardiomyocyte apoptosis induced by ADM by suppressing the PI3K/AKT/Bcl-2 pathway.

Keywords: Adriamycin; apoptosis; cardiomyocytes; PI3K/AKT/Bcl-2; propofol

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Introduction

Anthracyclines (ANTs) are commonly used in the chemotherapy of various malignant tumors, both solid and hematological, because they are highly potent and effective cytotoxic drugs, but their use is limited by their dose-dependent cardiotoxicity (1). Reportedly, 10–20% of patients experience cardiac dysfunction in the first year after ANT treatment and nearly 2–5% have symptomatic heart failure (2,3). The mechanism underlying ANTs [including adriamycin (ADM)]-induced cardiotoxicity is multifactorial and incompletely understood (4). Oxidative stress is thought to be primarily responsible, because myocardial tissues lack sufficient antioxidant mechanisms (5,6). ANTs increase the concentration of oxygen free radicals and induce lipid peroxidation, which destroys the structure and functional integrity of myocardial cells and causes myocardial damage (7,8). It has been demonstrated that ANTs interact with topoisomerase, which is key to the drugs' antitumor and also relevant for cardiotoxicity (9). Other mechanisms include calcium overload, iron metabolism disorder, suppression of the cardiac-specific gene expression program and inhibition of the expression of several sarcomeric proteins (10). Other research indicated that cardiomyocyte apoptosis is involved in the cardiotoxicity of ANTs (11), which we had previously reported in rat cardiomyocytes (12,13).

Propofol (2, 6-diisopropylphenol), as an intravenous sedative-hypnotic agent, is widely used for both induction/maintenance of anesthesia and sedation. It has pluripotent cytoprotective properties against various extrinsic insults including anti-inflammatory, antioxidant and cardioprotective effects (14,15), which could attentuate cardiac myocyte apoptosis by ischemia/reoxygenation (I/R) (16). The release of proinflammatory cytokines is inhibited by propofol, could reduce oxidative stress (17). The phosphatidylinositol 3 kinase/protein kinase B (PI3K/AKT) signaling pathway is involved in the regulation of oxidative stress and inflammatory response. These findings suggest that propofol could ameliorate the adverse effects of ANTs on myocardial cells. In this context, we explored the protective effect and mechanism of propofol on ANT-induced myocardial apoptosis *in vivo*.

We focused on the role of PI3K/AKT signaling pathway in ANT-induced myocardial apoptosis, which could explain the protective effect of propofol and provide a theoretical basis for it to be used as a routine anesthetic for neoadjuvant chemotherapy (NAC) in patients with advanced cancer in clinical practice. We present the following article in accordance with the ARRIVE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1549/rc).

Methods

Reagents

Propofol was purchased from Sigma-Aldrich (Missouri, MO, USA). ADM (active ingredient doxorubicin) was purchased from Haimen Pharmaceutical (Wenzhou, Zhejiang, China). Malondialdehyde (MDA) test kits and superoxide dismutase (SOD) assay kits were provided by Jiancheng Bioengineering Institute (Nanjing, Jiangsu, China). Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and cardiac troponin I (cTnI) enzyme linked immunosorbent assay (ELISA) kits of rat serum were purchased from R&D Systems (Minneapolis, MN, USA). Anti-PI3K-110α, pAKT-Ser473 and B cell lymphoma 2 (Bcl-2) antibodies were purchased from Cell Signaling Technology (Danvers, MA. USA). All other agents were from the Key Laboratory of Tianjin Medical University Cancer Institute and Hospital (Tianjin, China).

Animals

All experimental protocols involving the use of animals were reviewed and approved by the Animal Ethical Welfare Committee of Tianjin Medical University Cancer Institute and Hospital (Approved Certification No. AE-2020182), in compliance with Chinese national guidelines for the care and use of animals. The 40 F344 rats (female, 200–250 g, 9-week-old) were purchased from Peking University Medical College Laboratory Animal Science Center (Beijing, China) [License No. SCXK (Jing) 2006–2008]. All animals were maintained under the same conditions in a naturally ventilated room with a 12 h light/dark cycle, room temperature of 25–28 ℃, relative humidity 70–85% and were weighed once a week.

Animal experimental protocol

According to our previous methods (12,13), the F344 rats were randomly divided 4 groups (n=10): Control (saline injection of the same volume as treatment); ADM (injection of 0.8 mg/kg adriamycin); Prop (injection of 50 mg/kg propofol); and ADM + Prop (injection of 0.8 mg/kg adriamycin and 50 mg/kg propofol). The drugs were injected intraperitoneally every 3 weeks for six cycles.

The psychological status, appetite and activity of the rats in each group were observed. At 21 days after the last injection, the rats in the different treatment groups were humanely killed. The researchers who analyzed the data were unaware of the group allocation. A protocol was prepared before the study without registration.

Serum markers

At baseline, before the 4th injection and before death, blood samples were collected from caudal tail veins, while the rats were anesthetized by 2% pentobarbital sodium intraperitoneally. The serum level of SOD was determined by the xanthine oxidase method, and the serum level of MDA was detected with thiobarbituric acid method, and ELISA kits were used to detect the serum levels of ANP, BNP and cTnI at the different time points.

Histopathological examination by hematoxylin-eosin (HE) staining

After the rats were killed, the free wall of the left ventricle was excised: one half was fixed in 10% neutral formaldehyde solution and then in paraffin. The paraffin blocks were serially sectioned onto slides, routinely dewaxed and stained separately in Harris hematoxylin for 5 min, 1% hydrochloric acid alcohol for 5–10 s, rinsed with tap water for 25 min and then 0.5% eosin for 2–3 min. The Billingham scoring method was used to calculate the pathological score: the percentage of myocardial damage was determined by the percentage of myocardial cells with vacuole formation and/or muscle fiber loss.

Apoptosis

The remaining half of the myocardial tissue was minced aseptically to 1 mm^3 and digested with collagenase II (1 mg/mL) combined with hyaluronidase (0.2 mg/mL) for 1–2 h to create a single-cell suspension. Part of the suspension was mixed with Annexin V-fluorescein isothiocyanate (FITC) and propidium iodide (PI), incubated for 5–15 min at room temperature without light and then the proportion of apoptotic cells was analyzed by flow cytometry within 1 h.

Western blot

After washing the remaining single-cell suspension in phosphate-buffered saline (PBS) three times, cells were lysed in RIPA buffer (1 M Na_3VO_4, 1 M NaF, 1% NP40, 0.5 M PMSF). We used the Pierce™ BCA Protein Assay Kit (Thermo, USA) to assess the concentrations of proteins. After being run on 10% SDS-PAGE, the samples with 30 μg protein were transferred to polyvinylidene difluoride membranes electrophoretically. The membranes were incubated with the following primary antibodies: PI3K p110α (1:500), pAKT-Ser473 (1:2,000), and Bcl-2 (1:1,000). The next day, the membranes were probed and incubated with secondary antibody (CST, USA). The targeted bands were analyzed by Image J.

Statistical analysis

We analyzed all data using SPSS 26.0 software. All measurement data are presented as mean ± SD. The unpaired *T* test was used to compare differences of body weight in the different groups. For serum markers, apoptosis and protein expression analyses, Student's *t*-test was performed to compare the difference between two groups.

Results

General condition of rats in different groups

During establishment of the myocardial injury model, all 40 female rats that underwent injection of the different drugs survived. After the second cycle of administration, rats in both the ADM and ADM + Prop groups were observed to gradually experience food reluctance, slowing activity, hair loss, increased eye secretions and diarrhea, while the rats in the Prop group showed no physical or mental symptoms. Before the experimental process at baseline, there was no statistical difference in the body weight among the different treatment groups ($P>0.05$). Compared with the Control group, the body weights of rats in the ADM and ADM + Prop groups decreased significantly ($P=0.0011$ and $P=0.0041$, respectively) (*Figure 1A*). There was no significant difference between the ADM and ADM + Prop groups ($P<0.05$).

Effect of propofol on serum markers

At baseline, the serum levels of SOD, MDA, ANP, BNP and cTnI were not statistically significant among the different groups. Compared with the control group, the

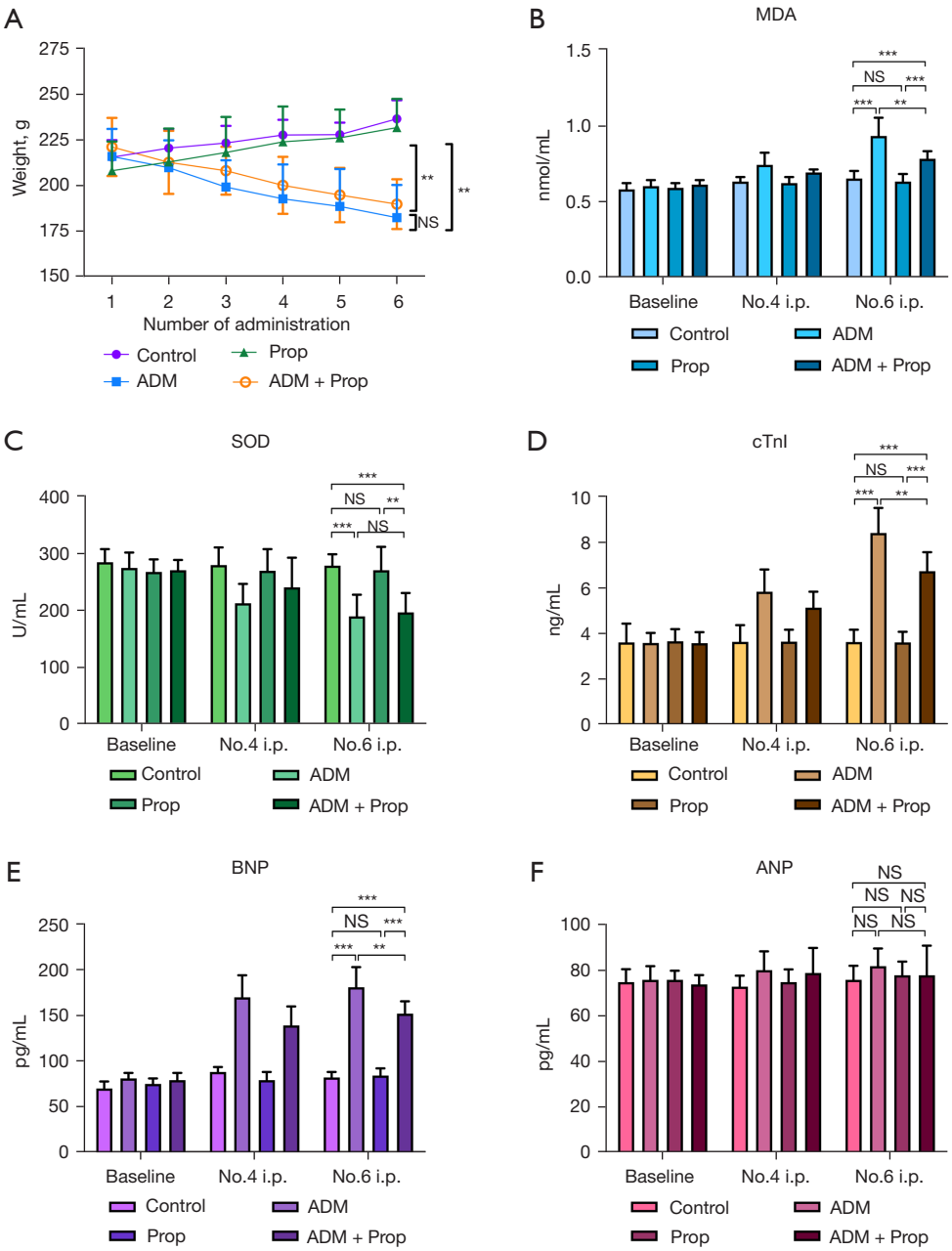

Figure 1 Effect of propofol on ADM-induced changes in body weight and serum biomarkers in rats. (A) Effect of the different treatments on body weights of rats in the 4 groups. (B-F) Effect of different treatments on serum levels of MDA, SOD, cTnI, BNP and ANP at baseline, 4th and 6th intraperitoneally injection. Each column or point represents the mean ± SD. The statistical analysis of serum biomarkers was performed by Student's *t*-test; for body weight, statistical significance was determined by unpaired *t*-test. NS: not significant, **P≤0.01, and ***P≤0.001. ADM, adriamycin; Prop, propofol; MDA, malondialdehyde; SOD, superoxide dismutase; cTnI, cardiac troponin I; BNP, B-type natriuretic peptide; ANP, atrial natriuretic peptide; i.p., intra-peritoneal.

concentrations of MDA, cTnI and BNP in both the ADM and ADM + Prop group were significantly higher after 6 cycles of injections. When compared with the ADM group, the levels of MDA, cTnI and BNP in the ADM + Prop group were significantly decreased (P=0.0033, 0.0014 and 0.0029 for MDA, cTnI and BNP respectively). Compared with the control group, the levels of SOD in the ADM and ADM + Prop groups were deceased (P<0.0001) and there was no significant difference between the ADM and ADM + Prop groups (P=0.6694) (*Figure 1B-1E*). For the serum ANP levels, there was no significant difference observed among the 4 different groups (*Figure 1F*).

Effect of propofol in ADM-induced myocardial damage

To further support the results of the biochemical assays, H&E staining of myocardial tissue from the rats in the different treatment groups was performed to assess the extent of damage. Under microscopy, cardiomyocytes showed vacuolar degeneration and edema of differing extent and infiltration of inflammatory cells, which made the intercellular space obviously wider (*Figure 2A*), which indicated the successful establishment of the myocardial injury animal model. Compared with the ADM group, the propofol group did not show the severe damage seen in the ADM + Prop group (P=0.0078) (*Figure 2B*).

Effect of propofol in ADM-induced apoptosis of cardiomyocytes

In order to define whether propofol protected against apoptosis of myocardial cells, the proportion of apoptotic cells in the different treatment groups as analyzed by flow cytometry (*Figure 2C*). The ratio of apoptotic cells was significantly upregulated to 23.3%±5.3% in the ADM group compared with 2.7%±0.75% in the Control group (P<0.0001). A significantly greater decrease in apoptosis in the combination treatment group compared with the ADM group (P=0.0388) (*Figure 2D*) was observed, which suggested that propofol had reduced the ADM-induced apoptosis of cardiomyocyte *in vivo*.

Effect of propofol on AD- induced activation of PI3K/AKT/Bcl-2 pathway

To ascertain the role of propofol in ADM-induced PI3K/AKT pathway activation in cardiomyocytes, the expression of PI3K p110α, pAKT-Ser473 and Bcl-2 in the different treatment groups was assessed by western blot (*Figure 3A*). PI3K p110α and pAKT-Ser473 were significantly overexpressed in the ADM group (P=0.0065 and P<0.0001 respectively) and Bcl-2 was downregulated (P<0.0001) compared the Control group. The expression of PI3K p110α and pAKT-Ser473 in the ADM + Prop group was significantly reduced compared with the ADM group (P=0.0161 and P<0.0001 respectively), which indicated that propofol could inhibit PI3K/AKT activation induced by ADM (*Figure 3B*,*3C*). The increase in Bcl-2 expression in the ADM + Prop group was statistically significant compared with the ADM group (P=0.0003) (*Figure 3D*). The findings showed that propofol could downregulate PI3K/AKT pathway activation induced by ADM in cardiomyocytes in vivo.

Discussion

Associated with intensive chemotherapy drugs, cardiotoxicity is a common lethal complication in the growing population of cancer survivors (18-20). The ANTs are among the most cardiotoxic, and are associated with dose-related cardiomyocyte injury and death leading to left ventricular dysfunction and heart failure (21). Currently, prevention and treatment of ANT-induced cardiotoxicity are still unmet clinical applications. Our aim was to investigate the protective effects and mechanisms of propofol in ADM-induced apoptosis of cardiomyocytes *in vivo*.

Extensive research has reported that oxygen free radicals play an important role in the development and progression of cardiotoxicity (22). Oxidative stress can be evaluated by measuring the serum levels of SOD and MDA, and our results from a rat model of myocardial injury revealed a reduction of SOD and an elevation of MDA in the serum of the ADM group compared with the Control group. Sheibani *et al.* reported a similar result; in their research, cardiac MDA and SOD content were significantly increased and decreased respectively by ADM treatment in comparison with the normal group (23), which indicated that ADM mediates cardiotoxicity via destabilization of the balance between reactive oxygen species and antioxidant enzymes (24,25). Our present study showed no difference in SOD levels between the ADM and ADM + Prop groups and a significant reduction in MDA in the ADM + Prop group compared with the ADM group, which suggested that propofol suppresses the production of oxygen free radicals (such as MDA) and thus protects the integrity of cardiomyocytes (12). The most commonly used circulating

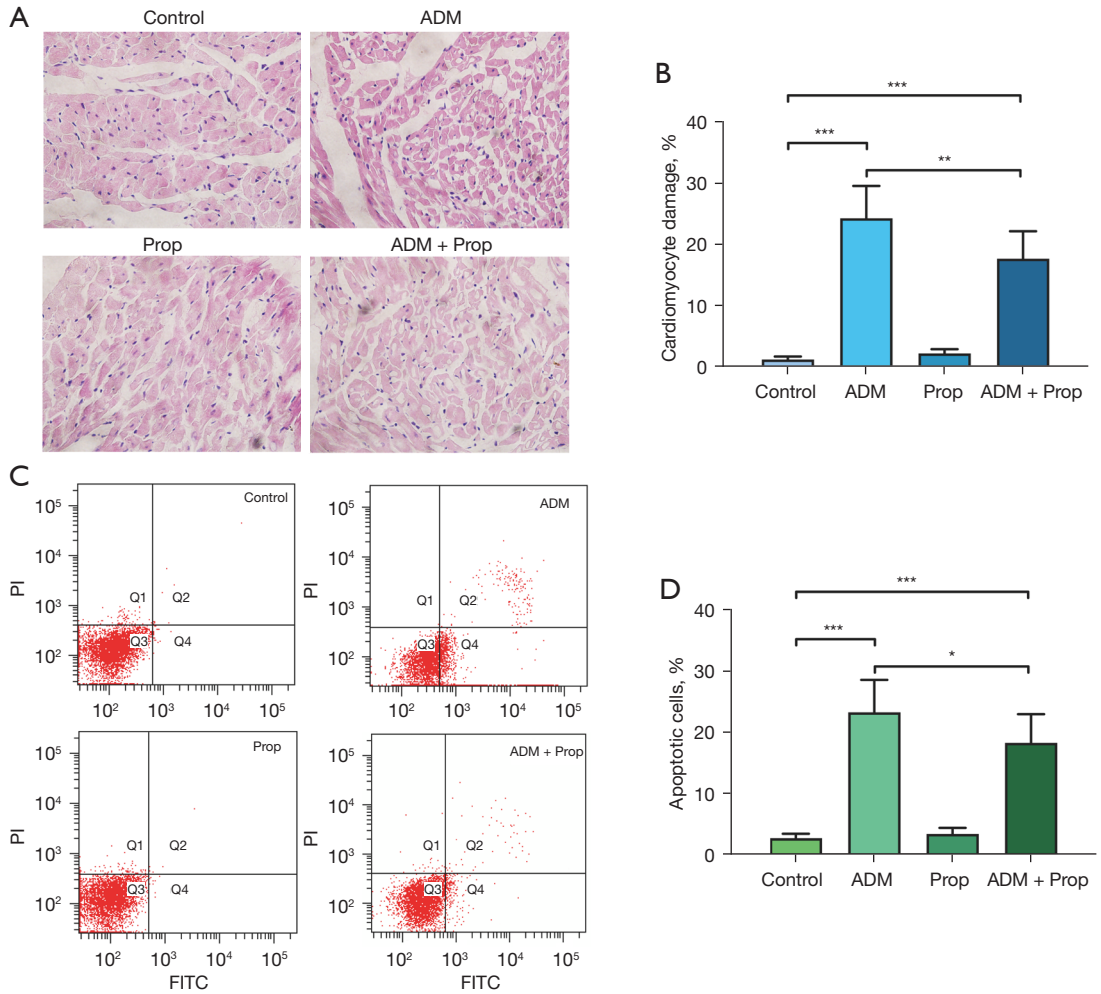

Figure 2 Effect of propofol on ADM-induced cardiomyocyte apoptosis in rats. (A) Morphology by HE staining of myocardial tissue samples from the 4 different groups of rats (Control, ADM, Prop and ADM + Prop) after 6 cycles of injection in group (original magnification ×400). (B) Statistical graph of cardiomyocyte damage in the different groups. Compared with in the ADM group, propofol counteracted the severe damage induced by ADM in the ADM + Prop group (P=0.0078). (C) Flow cytometric analysis of apoptotic cardiomyocytes in the different treatment groups. (D) Percentage of apoptotic cardiomyocytes in the different treatment groups by flow cytometry. Each column represents the mean ± SD. The statistical analysis was performed with Student's *t*-test. *P≤0.05, **P≤0.01, and ***P≤0.001. ADM, adriamycin; Prop, propofol; HE, hematoxylin-eosin; PI, propidium iodide; FITC, fluorescein isothiocyanate.

marker of the onset of ADM-induced cardiotoxicity is cTnI (26,27), which is used by clinicians to establishing the cardiac-monitoring schedule of ADM-treated patients (28). In addition, BNP, as a biomarker of congestive heart failure, is used to predict and monitor chemotherapy-related cardiac toxicity (29). In the present study, after 6 cycles of administration, the difference in the levels of cTnI and BNP between the ADM and ADM + Prop groups was statistically significantly decreased, which further confirmed the protective effect of propofol in ADM-induced cardiomyocyte injury.

Apoptosis, the complicated process of deliberate death of cells in multicellular organisms, is responsible for the programmed culling of cells during normal eukaryotic development and maintenance of organismal homeostasis (30). Our results of flow cytometry showed that ADM-induced cardiomyocyte apoptosis, revealing apoptosis as one of the major contributors to ADM-induced cardiac toxicity (*Figure 2*). Blocking apoptosis could prevent the loss of contractile cells and minimize myocardial injury after

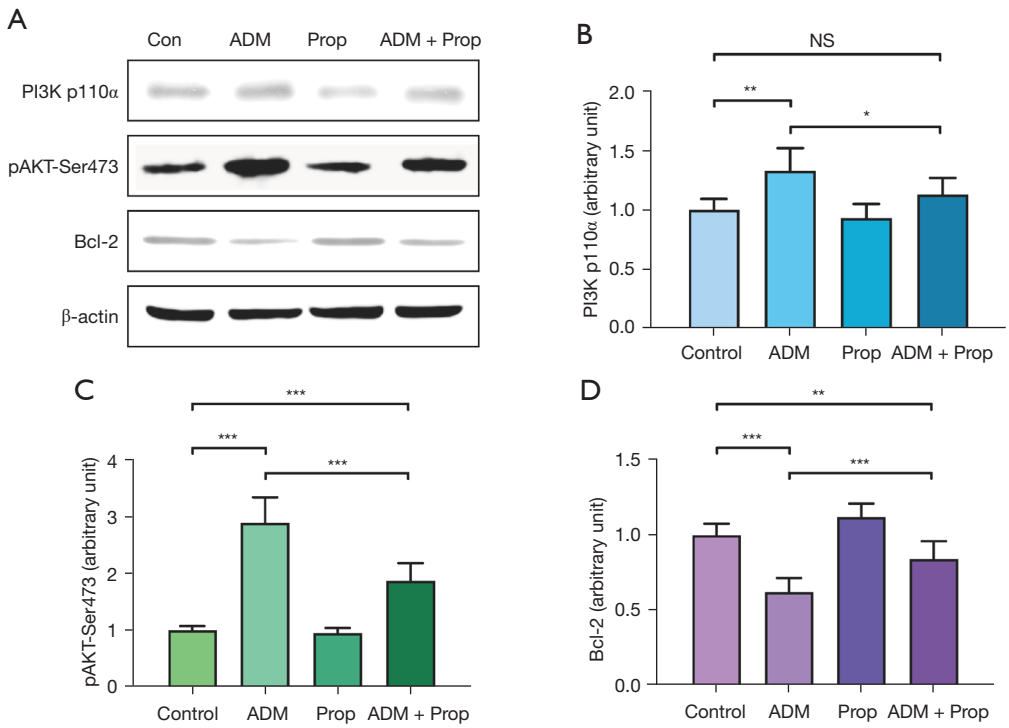

Figure 3 Effect of propofol on ADM-induced activation of PI3K/AKT/Bcl-2 pathway. (A) Levels of PI3K p110α, pAKT-Ser473 and Bcl-2 proteins tested by western blot. (B-D) Quantization map of the levels of PI3K p110α, pAKT-Ser473 and Bcl-2 proteins, relative to β-actin expression. Each column represents the mean ± SD. The statistical analysis was performed with Student's *t*-test. NS: not significant, *P≤0.05, **P≤0.01, and ***P≤0.001. ADM, adriamycin; Prop, propofol; PI3K, phosphatidylinositol 3 kinase; AKT, protein kinase B; Bcl-2, B cell lymphoma 2.

ADM treatment (31). Consistent with a previous report (13), we also revealed that propofol significantly attenuated ADM-induced cardiomyocyte apoptosis, implying that inhibition of apoptosis contributes to the mechanism by which propofol restrains the extent of ADM-induced myocardial toxicity (32).

The Bcl-2 family of proteins contains both pro-apoptotic and pro-survival members that balance the decision between cellular life and death (33), which regulates apoptosis (34). It has been reported that the PI3K/AKT signaling pathway both directly and indirectly regulates the functions of Bcl-2 proteins and consequently protects cells from apoptosis (35). ADM is known to modulate the PI3K/AKT signaling pathway, which may contribute to its cardiotoxicity (36). Dephosphorylation of PI3K/AKT after ADM exposure may lead to activation of apoptotic pathways (37). Conversely, activation of PI3K signaling has been demonstrated to ameliorate ADM-induced cardiomyopathy *in vivo* (35).

Propofol is a short-acting intravenous anesthetic agent that causes few side effects and thus has a favorable safety profile. It has been shown to be cardioprotective in experimental studies and in some small clinical trials of cardiac surgery using cardiopulmonary bypass. For myocardial I/R injury, propofol possesses an antioxidant property and activates multiple pro-survival signaling pathways including the PI3K/AKT/Bcl-2 pathway (30). It is also reported that propofol showed neuroprotective effects against neuronal apoptosis by increasing Bcl-2 expression (38). In another study (39), propofol protected cardiac H9c2 cells from hydrogen peroxide-induced injury by triggering the activation of AKT and parallel upregulation of Bcl-2 *in vitro*. The protective mechanism of propofol in ADM-induced cardiomyocyte apoptosis is unclear, but because it is known to exert a cardioprotective effect in ADM-imposed cardiac toxicity *in vitro* (40,41), we explored whether it could protect cardiomyocytes from apoptosis by suppressing the PI3K/AKT/Bcl-2 pathway *in vivo*. Consistent with our hypothesis, PI3K p110α and pAKT-Ser473 were significantly overexpressed in the ADM group and Bcl-2 was downregulated compared with the

Control group. Both proteins in the ADM + Prop group were significantly downregulated compared with ADM treatment. Compared with the ADM group, the increase in Bcl-2 expression in the ADM + Prop group was statistically significant, which clarified that propofol can effectively reduce cardiomyocyte apoptosis caused by ANTS *in vivo* by specifically inhibiting PI3K/AKT/Bcl-2.

In summary, our study results suggest that the protective role of propofol on cardiomyocyte apoptosis induced by ADM involves suppressing the activation of the PI3K/AKT/Bcl-2 pathway.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the ARRIVE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1549/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1549/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1549/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All experimental protocols involving the use of animals were reviewed and approved by the Animal Ethical Welfare Committee of Tianjin Medical University Cancer Institute and Hospital (Approved Certification No. AE-2020182), in compliance with Chinese national guidelines for the care and use of animals.

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