

## Effects of medetomidine on intra-renal arteries resistive and pulsatility indices in clinically normal adult domestic shorthair cats

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Article Info	Abstract
<p><b>Article history:</b></p> <p>Received: 09 October 2017 Accepted: 01 November 2017 Available online: 15 June 2018</p> <p><b>Key words:</b></p> <p>Cat Doppler Medetomidine Renal arteries Vascular ultrasonography</p>	<p>The aim of this study was to determine the effects of intramuscular injection of medetomidine on intra-renal arteries resistive and pulsatility indices by duplex Doppler ultrasonography in clinically normal adult domestic shorthair cats. For this purpose, twenty-six neutered adult healthy domestic shorthair cats (13 females and 13 males) were evaluated. B-mode, color Doppler and pulsed wave Doppler ultrasonography of right and left kidneys were performed to record the resistive index (RI) and pulsatility index (PI) of intra-renal arteries. To minimize statistical errors, the mean RI and PI were determined for each kidney by averaging three waveforms from the intra-renal arteries. Twenty-four hr later, the cats were sedated by 0.04 mg kg<sup>-1</sup> intramuscular administration of medetomidine. All the Doppler measurements were repeated 15 min after drug administration. Mean <math>\pm</math> standard deviation (SD) of PI and RI of the intra-renal arteries before administration of intramuscular medetomidine were <math>1.03 \pm 0.08</math> and <math>0.61 \pm 0.02</math>, respectively. Fifteen min after medetomidine administration, the mean <math>\pm</math> SD of PI and RI values were <math>1.04 \pm 0.08</math> and <math>0.61 \pm 0.02</math>, respectively. Significant differences were not detected in mean PI and RI values before and 15 min after drug administration. Our findings showed that intramuscular administration of medetomidine does not cause significant hemodynamic changes in the intra-renal arteries after 15 min.</p> <p style="text-align: right;">© 2018 Urmia University. All rights reserved.</p>

### تأثیر مدتومیدین بر روی شاخص های مقاومتی و ضربانی شریان های داخل کلیوی در گربه های سالم بالغ مو کوتاه اهلی

#### چکیده

هدف این مطالعه تعیین اثرات تزریق داخل عضلانی مدتومیدین بر روی شاخص های مقاومتی و ضربانی شریان های داخل کلیوی در گربه های سالم بالغ مو کوتاه اهلی توسط اولتراسونوگرافی داپلر بود. برای این منظور، ۲۶ قلابه گربه مو کوتاه اهلی سالم بالغ عقیم شده (۱۳ قلابه ماده و ۱۳ قلابه نر) مورد ارزیابی قرار گرفتند. اولتراسونوگرافی مد روشنایی، داپلر رنگی و داپلر موج ضربانی کلیه های راست و چپ جهت ثبت شاخص مقاومتی (RI) و شاخص ضربانی (PI) شریان های داخل کلیوی انجام پذیرفت. جهت به حداقل رساندن خطاهای آماری، متوسط RI و PI برای هر کلیه، به واسطه محاسبه میانگین سه موج از شریان های داخل کلیوی تعیین گردید. پس از ۲۴ ساعت، آرامبخشی گربه ها توسط تجویز داخل عضلانی ۰/۰۴ میلی گرم به ازای هر کیلوگرم وزن بدن مدتومیدین صورت پذیرفت. پانزده دقیقه پس از تجویز دارو، تمامی اندازه گیری های داپلر تکرار گردید. میانگین  $\pm$  انحراف معیار مربوط به RI و PI شریان های داخل کلیوی قبل از تجویز داخل عضلانی مدتومیدین به ترتیب  $1.03 \pm 0.08$  و  $0.61 \pm 0.02$  بود. پانزده دقیقه پس از تجویز مدتومیدین، میانگین  $\pm$  انحراف معیار مربوط به RI و PI به ترتیب  $1.04 \pm 0.08$  و  $0.61 \pm 0.02$  بود. تفاوت معناداری در میانگین مقادیر RI و PI قبل و ۱۵ دقیقه پس از تجویز دارو مشاهده نشد. نتایج نشان داد که تجویز داخل عضلانی مدتومیدین، تغییرات همودینامیک عمده ای را در شریان های داخل کلیوی پس از ۱۵ دقیقه موجب نمی شود.

**واژه های کلیدی:** اولتراسونوگرافی عروقی، داپلر، شریان های کلیوی، گربه، مدتومیدین

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## Introduction

Evaluation of renal hemodynamic parameters including blood flow, peak systolic velocity and mean and end diastolic velocities as well as resistive index (RI) and pulsatility index (PI) by Doppler technique is used in both human and veterinary medicine.<sup>1-7</sup> Additionally, color and power Doppler ultrasonography have been used for hemodynamic effects assessment of pharmacological agents.<sup>6,8</sup> The normal kidney's vascular bed has a low effective resistance to blood flow which is revealed by constant forward flow during diastole.<sup>9,10</sup> The RI of intra-renal arteries (interlobar or arcuate) probably yields the most reliable results and Doppler parameters are most commonly used for clinical investigations of renal diseases.<sup>4,7</sup> In human patients, RI and PI increases at the level of interlobar arteries have been reported to be associated with increase of severity and time of hypertension.<sup>11,12</sup> The RI is also considered as an indicator of renal function in patients with chronic renal diseases.<sup>13</sup>

In cats and dogs, the intra-renal RI determination by duplex Doppler is helpful in renal disease exploration, in which the kidney has an ordinary greyscale ultrasonographic appearance or when the only notable renal parenchymal abnormality is augmented renal cortex echogenicity.<sup>14</sup> Persistent hypertension can damage kidney resulting in glomerular diseases in dogs and cats.<sup>15,16</sup> Although no association has been found between either renal PI or RI and systemic blood pressure in dogs and cats, a positive linear relationship has been reported between an increase in these renal indices and serum creatinine or urea levels in cats with renal diseases.<sup>16</sup>

In both human and veterinary medicine, RI and PI are valuable indicators of vascular resistance. Once the vascular resistance increases due to vessel obstruction or vasoconstriction, diastolic blood flow falls more than the systolic one.<sup>17</sup> This fact leads to greater reduction of the end diastolic velocity as compared with peak systolic velocity and therefore, RI and PI will rise.<sup>16</sup>

In the renal diseases, alterations in PI and RI have been reported in dogs and cats.<sup>16,18</sup> A number of studies indicated an increase in RI values of intra-renal arteries in dogs with ureteral obstruction and also in cats with acute and chronic kidney diseases, obstructive renal disease and acute tubular necrosis.<sup>16,19-21</sup> In addition, administration of sedatives or anesthetic agents may change these indices.<sup>22,23</sup> However, using these indices as prognostic factors needs further investigation in dogs and cats, the side effects of such sedatives and anesthetics should be always considered.

Alpha-2 agonist drugs including medetomidine hydrochloride are generally utilized in small animals as pre-anesthetic agents due to their sedative, analgesic, anxiolytic and muscle relaxant properties.<sup>24,25</sup> Medetomidine has several side effects such as bradycardia,

decreased respiration, hypothermia and vomiting.<sup>26</sup> Despite these side effects, the main advantage of this drug is its reversibility after atipamezole administration.<sup>25</sup> The effect of medetomidine on systemic blood pressure is variable; it may cause temporary blood pressure elevation due to its influence on the peripheral alpha-2 adrenoceptors followed by decreased heart rate and low blood pressure.<sup>26-29</sup> The recommended dose range of medetomidine in cats is 10 to 40  $\mu\text{g kg}^{-1}$  bodyweight (BW), intravenous (IV) and 40 to 80  $\mu\text{g kg}^{-1}$  BW, intramuscular (IM).<sup>27</sup> The onset of drug's action occurs in 1 to 5 min after IV administration and 5 to 15 min after IM administration.<sup>25,27,30</sup> The drug is rapidly absorbed after IM administration and the peak plasma level achievement time is within 30 min.<sup>31</sup>

The objective of the current study was to evaluate the intra-renal arteries' resistive and pulsatility indices in clinically normal adult domestic shorthair cats, before and after medetomidine sedation. To the best of the authors' knowledge, this is the first report regarding the effects of medetomidine administration on intra-renal arteries' indices in healthy adult domestic shorthair cats.

## Materials and Methods

The experiment was carried out under supervision of the ethics committee of Islamic Azad University science and research branch based on Iranian ethical codes for studies on laboratory animals (IR.IAU.SRB.REC.1395.49).

Over a period of 6 months in 2016, we selected 26 neutered adult healthy domestic shorthair cats (13 females and 13 males). The included animals were client-owned and clinically normal without apparent disease. It was noticed that they had not recently received any medication. They were fed on a commercial cat diet by their owners. Water was available for the studied cats *ad libitum*. Consent form was signed by clients prior to enrolling their cats in this study.

A full physical examination was performed by an expert veterinary internist and the cats were selected based on their normal physical, complete blood count and biochemistry profile, urinalysis and abdominal ultrasonography. Cardiac examinations including auscultation, electrocardiography and echocardiography were also performed and the results indicated healthy cardiac function and no occult heart disease. To follow a standard ultrasonographic approach and minimize various artifacts caused by gastrointestinal contents and hair coat, the cats were kept fasting for at least 12 hr and ventral abdominal hair was clipped prior to ultrasonography. Water was available for all animals during the fasting hours. To reduce physiological and behavioral responses to stress that might supervene after hair clipping; the cats were placed in their carriers for 5 to 10 min regarding environmental adaption preceding examination.

All ultrasonography examinations were performed by duplex Doppler ultrasonography machine (E30; VINNO, Beijing, China) with 4.5 to 18 MHz frequency linear transducer. B-mode, color Doppler and pulsed wave Doppler ultrasound examinations were performed on both kidneys to assess RI and PI of the intra-renal arteries (Fig. 1).

Renal B-mode imaging was obtained while the cats were in dorsal or lateral recumbency and renal scanning was done in both transverse and sagittal planes.<sup>32</sup> All portions of right and left kidneys including cortex, medulla and collecting system were fully assessed and no abnormal lesion was detected ultrasonographically in renal parenchyma. Renal length and height were measured in sagittal plane. To visualize the intra-renal vasculature of both kidneys, color Doppler mapping was used. Additional information on Doppler flow spectra was obtained by placing 1 to 2 mm sample gate near the renal hilum. The angle between ultrasound beam and vessel's direction in all stages of the study was less than 65 degree. To minimize statistical errors, mean RI and PI of each kidney were determined by averaging three waveforms from the intra-renal arteries in three different anatomic areas.

During ultrasonographic investigation, several machine adjustments were applied based on the animal's body condition score to optimize image quality. Wall filter and pulse repetition frequency were adjust on the lowest value to reduce aliasing artifact. Peak systolic and end-diastolic velocities were also measured manually (using calipers) from recorded spectra. The PI and RI were determined automatically by the ultrasound machine.

Twenty-four hour later and at the same time of the day, the cats were sedated by 0.04 mg kg<sup>-1</sup> IM administration of medetomidine (Laboratories Syva S.A.U., León, Spain).<sup>30</sup> We chose this dose because in our clinical experience it allowed sedation for sufficient time for routine ultrasonographic examinations. Each cat was moved into a cage after drug administration and kept in a quiet room to

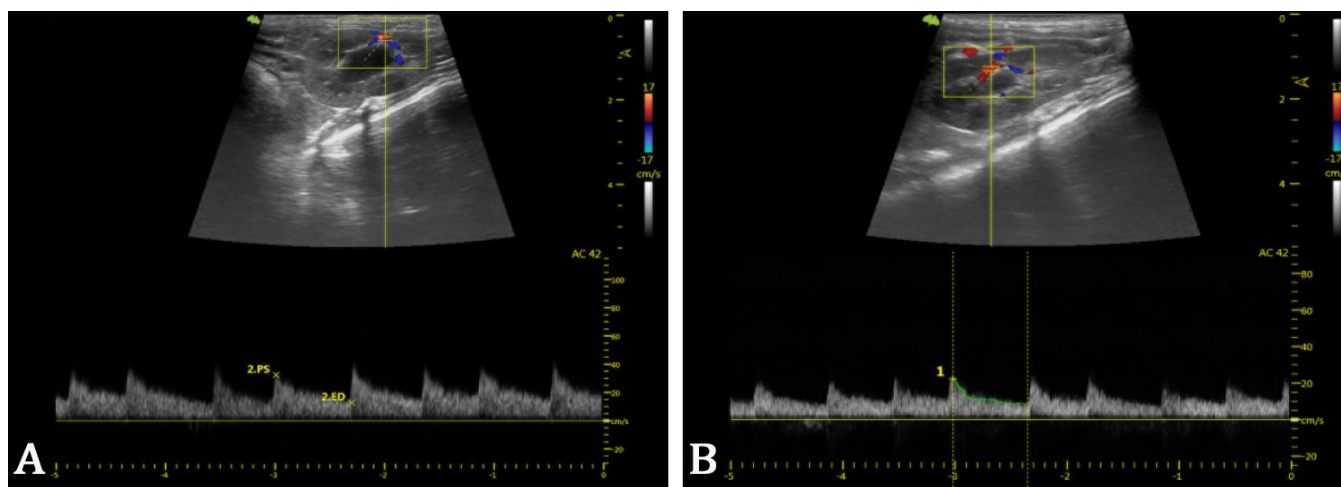
minimize stress and excitement until it became recumbent. All aforementioned measurements except renal dimensions were repeated 15 min after drug administration following onset of clinical sedation.<sup>25,30</sup> Heart rates were also recorded before injection (0 min) and 15 min after injection.<sup>25</sup> One examiner performed all the ultrasonographic examinations and measurements.

Statistical analysis was performed using SPSS statistical software program (version 20.0; SPSS Inc., Chicago, USA). To check data normality, the one-sample Kolmogorov–Smirnov test was used. The paired samples *t*-test was also used to compare the right and left renal RI and PI values. Mean and standard deviation (SD) were calculated for all kidneys combined and for the right and left kidneys separately. Differences in the mean RI and PI values before and after drug administration were analyzed by paired-sample *t*-test. An independent sample *t*-test was used to compare the mean RI and PI values for the animals' sex. Pearson's coefficient was used to evaluate the correlation between heart rate and mean RI and PI values after drug administration. A *p*-value less than 0.05 was considered statistically significant.

## Results

Twenty-six neutered adult healthy domestic shorthair cats (13 females and 13 males) with mean age of 2.50 years (1 to 5 years) and mean weight of 3.40 kg (2.00 to 5.50 kg) were enrolled in this study. Descriptive statistics of the measured parameters in the studied population are summarized in Table 1.

All numeric data recorded in the current study population were normally distributed according to one-sample Kolmogorov–Smirnov test ( $p > 0.07$ ). Mean  $\pm$  SD of heart rate before and after drug administration were 191.40  $\pm$  10.10 beat per min (bpm) and 109.20  $\pm$  8.80 bpm, respectively. Heart rate difference was statistically



**Fig. 1.** Intra-renal duplex Doppler ultrasonography of a domestic shorthair cat. A) Before drug administration B) 15 min after intramuscular injection of medetomidine.

**Table 1.** Descriptive statistical results of the intra-renal arteries indices in the clinically normal cats.

Parameters	Before medetomidine administration		95% CI	15 min after medetomidine administration		95% CI
	Mean	SD		Mean	SD	
LreRI	0.60	0.02	0.59-0.60	0.61	0.02	0.60-0.61
RreRI	0.61	0.02	0.60-0.61	0.61	0.02	0.60-0.61
LrePI	1.03	0.09	0.99-1.06	1.04	0.09	1.00-1.07
RrePI	1.03	0.09	0.99-1.06	1.04	0.09	1.00-1.07
ReRI	0.61	0.02	0.60-0.61	0.61	0.02	0.60-0.61
RePI	1.03	0.08	0.99-1.06	1.04	0.08	1.00-1.07
LKL (mm)	32.39	2.70	31.29-33.48	N/A	N/A	N/A
LKH (mm)	18.91	2.62	17.85-19.96	N/A	N/A	N/A
RKL (mm)	32.88	2.69	31.79-33.96	N/A	N/A	N/A
RKH (mm)	18.96	2.86	17.80-20.11	N/A	N/A	N/A
KL (mm)	32.63	2.52	33.61-33.64	N/A	N/A	N/A
KH (mm)	18.93	2.42	17.95-19.90	N/A	N/A	N/A

CI: Confidence interval, LreRI: Left intra-renal arteries resistive index, RreRI: Right intra-renal arteries resistive index, LrePI: Left intra-renal arteries pulsatility index, RrePI: Right intra-renal arteries pulsatility index, ReRI: Intra-renal arteries resistive index, RePI: Intra-renal arteries pulsatility index, LKL: Left kidney length, LKH: Left kidney height, RKL: Right kidney length, RKH: Right kidney height, KL: kidney length, KH: kidney height, N/A: Not Applicable.

significant ( $p < 0.001$ ). Mean  $\pm$  SD of PI and RI values of the intra-renal arteries in the study population before administration of IM medetomidine were  $1.03 \pm 0.08$  and  $0.61 \pm 0.02$ , respectively. Fifteen min after medetomidine administration, the mean  $\pm$  SD of PI and RI values were  $1.04 \pm 0.08$  and  $0.61 \pm 0.02$ , respectively. Significant differences were not found in mean PI and RI values before and 15 min after drug administration ( $p = 0.10$ ).

The RI values before and after medetomidine administration were  $0.61 \pm 0.02$  and  $0.61 \pm 0.02$  for males ( $p = 0.70$ ) and  $0.60 \pm 0.02$  and  $0.61 \pm 0.01$  for females ( $p = 0.80$ ), respectively. The PI values before and after medetomidine administration were  $1.04 \pm 0.11$  and  $1.05 \pm 0.10$  for males ( $p = 0.70$ ) and  $1.01 \pm 0.06$  and  $1.02 \pm 0.05$  for females, respectively ( $p = 0.70$ ).

Renal length and height were  $33.06 \pm 2.30$  and  $19.31 \pm 2.41$  for males and  $32.21 \pm 2.67$  and  $18.56 \pm 2.40$  for females, respectively. There was no statistical difference between males and females regarding renal length and height ( $p = 0.30$  and  $p = 0.50$ , respectively). Neither PI nor RI showed significant difference between the right and left kidney before and after drug administration ( $p > 0.63$ ).

## Discussion

Medetomidine is a highly specific  $\alpha_2$ -adrenoceptor agonist with lipophilic character and rapid and complete absorption after intramuscular injection producing dose-dependent sedation and analgesia.<sup>33</sup> Despite the beneficial effects in small animal patients, it entails major adverse effects for the cardiovascular system. Profound reduction in heart rate associated with bradyarrhythmias, hypertension followed by varying degrees of hypotension, increased systemic vascular resistance and central venous pressure and decreased cardiac output are concerning for small animal practitioners.<sup>27,34,35</sup>

Blood flow measurements in humans are feasible in non-sedated patients; however, in veterinary medicine it is sometimes necessary to sedate the patients for imaging due to their poor cooperation and aggressive temper, particularly when a thorough study such as abdominal vasculature ultrasonography is needed.<sup>4</sup> The RI and PI are considered as indirect sensitive indices showing the degree of vasoconstriction<sup>36</sup> and may be beneficial in renal function evaluation in dogs and cats.<sup>16,18</sup>

Mishina *et al.* have analyzed blood pressure (BP) in twenty unsedated cats during 24 hr with telemetry system for 20 days. They found that BP in cats has diurnal variations. Highest BP has been reported between 6:00 and 9:00 and between 16:00 and 20:00.<sup>37</sup> To minimize the possible variations associated with diurnal changes, all the measurements in our study were performed between 10:00 and 12:00 AM. To reduce the effect of stress on animal's blood parameters, the interval between the first and the second Doppler ultrasonography examinations considered 24 hr.<sup>38</sup>

In 2007, Novellas *et al.* have estimated intra-renal and ocular RI and PI in normal dogs and cats by pulsed wave Doppler ultrasonography. No substantial differences were detected between the values obtained for the right and left kidneys. The upper values of renal RI and PI in dogs were 0.72 and 1.52, respectively. For cats, renal RI and PI were 0.70 and 1.29, respectively. It was concluded that PI is more sensitive than RI for differentiating abnormal waveforms, because it shows the mean velocity during a single cycle.<sup>39</sup> The results of RI and PI in the present study, before and after IM medetomidine administration were within reported reference ranges of intra-renal arteries in cats and in spite of all the described cardiovascular changes after medetomidine administration,<sup>27</sup> our results were lower than the suggested cut-off values.<sup>39-42</sup>

Medetomidine prompts bradycardia because of presynaptic  $\alpha_2$ -receptors initiation in the central nervous

system and this is not likely interceded by mechanism of vagal reflex baroreceptor. Simultaneously, there is an increase in systemic vascular resistance due to the effect of medetomidine on peripheral  $\alpha_2$ -adrenoreceptors.<sup>29,43</sup> In feline species, the heart rate decreases between 30% and 50% with medetomidine sedation.<sup>25,27</sup> In our study, heart rate was decreased significantly following medetomidine administration and the results were consistent with findings of previous studies.<sup>25,27</sup>

The correlation between heart rate and RI have been evaluated in human and animals in several studies. In humans, heart rate has been reported to show negative correlation with RI.<sup>44</sup> In dogs and cats, Novellas *et al.* have also reported no inverse relationship between pulse rate and renal RI.<sup>39</sup> Mitchell and colleagues have found that in anesthetized cats, the heart rate does not have a significant effect on RI or PI.<sup>23</sup> Our finding is in agreement with the previous studies on cats and dogs.<sup>23,39</sup> According to our study, no statistically significant inverse relationship was found between measured intra-renal arteries RI or PI and the heart rate. We do not believe that the observed effect of medetomidine on heart rate in the current study population caused any significant alternation in intra-renal resistance or renal blood flow because kidney's blood flow is less affected by peripheral resistance, considering the dose and route of administration.<sup>27</sup>

Rivers *et al.* have estimated the RI in the arcuate arteries of sedated normal cats using duplex Doppler ultrasonography. They have found that in cats sedated by ketamine hydrochloride, RI value ranges between 0.52 and 0.60 for the left kidney and between 0.55 and 0.63 for the right kidney; nevertheless, no significance difference was noticed between the two kidneys.<sup>10</sup> The present study also showed no significant difference between the right and left kidneys' RI and PI. Tipisca *et al.* have assessed RI in normal cats and with renal disease. They have concluded that RI can be considered a valuable diagnostic tool in differentiating diffuse renal disease in cats. They have also stated that RI does not change with animal's age and RI may be different in right and left kidneys.<sup>42</sup>

In another study in 2008, Mino *et al.* studied the effects of medetomidine administration on the Doppler variables of abdominal arteries in healthy dogs; they have measured PI and RI of the abdominal aorta and renal, cranial mesenteric and celiac arteries. The authors have found that RI does not change in these vessels; however, a marked increase was noticed in the PI of abdominal aorta. They have also confirmed that medetomidine can be used as a good sedative agent for ultrasonographic evaluation of the abdominal vessels. Based on the report of these investigators, a possible explanation for lack of changes in renal arteries PI and RI may be that renal blood flow is less affected by peripheral resistance.<sup>6</sup>

Our results were consistent with the findings of Mino *et al.* on dogs. In both studies, RI and PI were altered after

medetomidine administration, but these changes were not clinically or statistically significant because peripheral resistance has a smaller effect on the renal blood flow, possibly explaining why the renal arteries did not show any changes in PI or RI.<sup>6</sup> Another likely reason for these findings is that the kidney is able to autoregulate its blood flow within certain limits of systemic arterial blood pressure and blood flow, in order to keep a constant level of glomerular filtration rate.<sup>45</sup>

The dose of medetomidine and route of administration are other key factors. In fact, at low doses that we used in our study, medetomidine affects more centrally, whereas at higher doses it may cause a more significant stimulation of peripheral adrenoceptor and vasoconstriction.<sup>27</sup> Also, noticeable changes in blood pressure can be avoided through IM administration of low-dose medetomidine.<sup>27</sup>

We only evaluated the effect of a single dose of medetomidine at one time point, which is the limitation of this study. Thus, further studies are recommended to assess the effect of different doses of medetomidine on intra-renal PI and RI at different time points in cats with normal kidney function and various renal diseases. Also, correlation and alteration of PI and RI should be evaluated with concomitant assessment of systemic blood pressure.

In conclusion, the results of the present study suggest that IM administration of medetomidine has minimal effect on intra-renal arteries' RI and PI and could be a suitable sedative for performing pulsed wave Doppler ultrasonography examination. Furthermore, use of this sedative/analgesic drug may be helpful in aggressive and painful feline patients which are not cooperative during abdominal ultrasonography. However, considering the limitations of the current study, further studies are recommended to obtain more detailed data.

### Conflict of Interest

The authors do not have any potential conflicts of interest to declare. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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