

# Effect of the extent of short-duration exercise stress combined with adenosine triphosphate on the artifacts of two different regions on myocardial perfusion single-photon emission computed tomography

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## Research article

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# Abstract

**Background:** We aimed to evaluate the differences in the reduction of undesired artifacts among different low-grade exercise stress levels combined with drug stress and their related factors by using myocardial perfusion single-photon emission computed tomography (SPECT) in patients with suspicious coronary artery disease.

**Methods:** We divided patients into 4 groups as follows: group A, adenosine triphosphate (ATP) for 6 min; group A+25 W, ATP+25 W exercise for 6 min; group A+35 W, ATP+35 W exercise for 6 min; group A+45 W, ATP+45 W exercise for 6 min) and enrolled only those whose summed stress scores were <3. Undesired artifacts were evaluated on the basis of heart-to-liver activity ( $H/L$ ) ratio and heart-to-10 pixels below the heart ( $H/\text{below the } H$ ) ratio.

**Results:** The logarithmic values of  $H/L$  and  $H/\text{below the } H$  ratios were significantly higher in groups A+35 W and A+45 W than in group A. In all the patients, the logarithmic values of  $H/L$  and  $H/\text{below the } H$  ratios positively correlated with heart rate ( $p=0.004$  and  $p=0.008$ , respectively), rate pressure product (RPP;  $p=0.005$  and  $p=0.008$ , respectively), and the increment of RPP ( $p=0.002$  and  $p=0.005$ , respectively) after stress in the univariate analysis. The left ventricular end-diastolic volume (LVEDV) after stress ( $p=0.002$ ) negatively correlated with the logarithmic value of  $H/\text{below the } H$  ratio, but not  $H/L$  ratio. Although male sex was independently associated with the logarithmic values of both  $H/L$  ( $p=0.014$ ) and  $H/\text{below the } H$  ratios ( $p=0.001$ ) in multivariate regression analysis, LVEDV was also independently associated with the logarithmic value of  $H/\text{below the } H$  ratio ( $p<0.001$ ).

**Conclusion:** ATP plus  $\geq 35$  W exercise stress for 6 min was useful for reducing undesired artifacts after stress in myocardial perfusion SPECT. LVEDV after stress was independently associated with the  $H/\text{below the } H$  ratio, but not the  $H/L$  ratio.

## Background

Streak artifacts are the most common source of error in myocardial single-photon emission computed tomography (SPECT) imaging. Stress with vasodilators has become increasingly used in myocardial perfusion SPECT, but the reduced activities in the inferior regions on SPECT images are explained by the liver-to heart artifact due to the intense tracer uptake in the liver [1, 2]. High liver activity adjacent to the inferior wall results from oversubtraction of the activity from the inferior wall. Myocardial uptake was greatest with administration of vasodilators than with exercise, and this effect was not attenuated by combining vasodilator administration with exercise [3]. Exercise stress is well known to increase heart-to-background count ratios as compared with drug stress alone and to reduce hepatic tracer uptake relative to the heart. Although adding low-level exercise stress to drug stress may help overcome some of the limitations of drug infusion alone and is useful for reducing the streak artifact [4–6], the appropriate extent of short-duration exercise stress remains controversial. However, no direct comparison has been made between the standard adenosine stress and the pharmacological stress combined with bicycle

exercise at various low grades. In this study, we hypothesized that a protocol combining a 6-min adenosine triphosphate (ATP) infusion with several different low-grade bicycle exercise protocols would improve streak artifacts among patients unable to generate an adequate stress during exercise, as compared with the standard ATP-only protocol. We evaluated the differences in the reduction of undesired artifacts between two different background regions and the related factors on myocardial perfusion SPECT in patients with suspicious coronary artery disease. We only included patients whose summed stress scores (SSSs) were  $< 3$  for a robust and accurate evaluation of artifacts.

## Methods

Subjects with suspected angina pectoris who were unable to generate adequate stress during exercise because of antianginal medications or confounding factors that might have hindered them from achieving the target heart rate underwent elective  $^{99m}\text{Tc}$ -tetrofosmin stress myocardial perfusion imaging (MPI). The patients ( $n = 280$ , from December 2015 to September 2017) were randomly allocated to one of the four stress protocols ( $n = 70$  each) as follows: ATP [7, 8] at  $120 \mu\text{g}/\text{kg}$  for 6 min (group A) and ATP at  $120 \mu\text{g}/\text{kg}$  for 6 min concomitantly combined with various exercise intensities for 6 min at 25, 35, and 45 W (groups A + 25 W, A + 35 W, and A + 45 W, respectively). The subjects exercised on a bicycle ergometer and received 110 MBq of  $^{99m}\text{Tc}$  tetrofosmin injection at 3 min after initiation of ATP infusion. Image acquisition was initiated 45 min after the  $^{99m}\text{Tc}$  injection. A 2-min planar image was obtained, followed immediately by the acquisition of a standard gated SPECT image. Perfusion imaging was performed using a 2-detector gamma camera (ADAC Forte), with a circular  $180^\circ$  orbit. The perfusion data were displayed in a 17-segment model in accordance with the American Society of Nuclear Cardiology guidelines [9]. The 17 segments for each image were scored from 0 to 4, with 0 indicating no perfusion defect and 4 indicating no tracer. In this study, we enrolled only patients whose SSSs were  $< 3$  because of robust clarification of artifacts. Therefore, we analyzed only the data of 109 patients (group A,  $n = 23$ ; group A + 25 W,  $n = 34$ ; group A + 35 W,  $n = 28$ ; and group A + 45 W,  $n = 24$ ). Whereas the stress and rest studies were interpreted together in the usual manner, the four-group images were analyzed in random order to avoid bias by the expert reader. The exclusion criteria were as follows: a contraindication to adenosine (moderate to severe chronic obstructive pulmonary disease or asthma, second- or third-degree atrioventricular block or sinus node disease, known as hypersensitivity to adenosine); hemodynamic instability; decompensated congestive heart failure; or the use of theophylline or dipyridamole within the preceding 48 h. This study complied with the tenets of the Declaration of Helsinki, and all patients provided written informed consent to participate.

Undesired background artifacts were evaluated using two different modes. To obtain the heart-to-liver activity ( $H/L$ ) ratio, the regions of interest were drawn around the heart and liver, excluding the gall bladder. "Heart counts" and "liver counts" were obtained from the point of maximum counts in each region of interest (Fig. 1). Undesired artifacts were also evaluated on the basis of heart-to-10 pixels below the heart ratio ( $H/\text{below the } H$  ratio). The profile lines were placed on the heart and below the heart from the bottom of the heart image to 10 pixels. "Heart counts" were obtained from the maximum count in the

profile line, and “below heart counts” were obtained from the minimum count in the profile line. These ratios were determined from the anterior planar images.

Continuous variables are expressed as means  $\pm$  standard deviations, whereas categorical variables are presented as percentages. Differences in categorical variables among the groups were assessed using chi-square tests ( $4 \times 2$ ), while those in continuous variables were assessed using one-way analysis of variance, and those between two groups were made using a post hoc Bonferroni test. The significance of the correlation between two variables was assessed with regression analysis. A p value of  $< 0.05$  was considered statistically significant.

## Results

The clinical characteristics of the patients are shown in Table 1. No significant differences in age, sex, incidence of comorbidities, medications, and laboratory data except for low-density lipoprotein cholesterol levels were found among the four groups. The values of the hemodynamic parameters were significantly higher in the groups with concomitant exercise than in those without exercise (Table 2). Although left ventricular end-diastolic volume (LVEDV), end-systolic volume, and ejection fraction were not significantly different among the four groups before and after the protocol in terms of SPECT data, the logarithmic value of the heart-to-background count ratios such as the *H/L* ratio and *H/below the H* ratio was significantly higher in groups A + 35 W and A + 45 W than in group A (Fig. 2).

Table 1  
Patient characteristics

	Group					p Value
	Total	A	A + 25W	A + 35W	A + 45W	
	n = 109	n = 23	n = 34	n = 28	n = 24	
Age, years	70 ± 10	75 ± 9	68 ± 10	69 ± 10	71 ± 8	0.056
Male, %	41	48	32	39	50	0.508
Previous MI, %	4	13	3	0	0	0.051
Previous PCI, %	16	39	12	11	4	0.051
Cerebrovascular disease, %	17	31	7	14	25	0.071
Peripheral artery disease, %	8	22	3	7	4	0.061
Hypertension, %	62	73	65	54	58	0.479
Dyslipidemia, %	57	68	62	46	54	0.051
Diabetes mellitus, %	41	46	38	46	33	0.782
Atrial fibrillation, %	5	9	3	7	0	0.445
Current Smoking, %	15	23	15	11	13	0.715
Laboratory data						
Hb, g/dL	13.6 ± 1.7	12.7 ± 1.7	13.6 ± 1.4	14.1 ± 1.9	13.9 ± 1.8	0.051
HbA1c, %	7.8 ± 2.6	6.7 ± 1.2	8.2 ± 2.7	8.4 ± 3.2	7.4 ± 2.5	0.216
UA, mg/dL	5.4 ± 1.5	5.1 ± 0.8	5.2 ± 1.5	5.8 ± 1.8	5.6 ± 1.8	0.415
LDL-C, mg/dL	122 ± 35	108 ± 29	122 ± 30	139 ± 35	113 ± 41	0.036
HDL-C, mg/dL	54 ± 26	53 ± 15	61 ± 41	51 ± 10	48 ± 20	0.493
Creatinine, mg/dL	0.92 ± 0.64	1.23 ± 1.15	0.77 ± 0.21	0.81 ± 0.37	0.97 ± 0.45	0.054
BNP, pg/mL	98.1 ± 140.2	180.6 ± 217.8	75.7 ± 86.3	81.2 ± 90.0	44.5 ± 44.8	0.067
Medications						
ADA, %	22	14	27	29	17	0.167
ATA, %	22	36	27	11	17	0.192

	Group					
<b>β blocker, %</b>	<b>14</b>	<b>14</b>	<b>18</b>	<b>18</b>	<b>4</b>	<b>0.440</b>
<b>CCB, %</b>	<b>46</b>	<b>55</b>	<b>47</b>	<b>46</b>	<b>38</b>	<b>0.634</b>
<b>Diuretics, %</b>	<b>8</b>	<b>14</b>	<b>6</b>	<b>11</b>	<b>4</b>	<b>0.374</b>
<b>Nitrates, %</b>	<b>7</b>	<b>14</b>	<b>9</b>	<b>7</b>	<b>0</b>	<b>0.636</b>
<b>RAS-I, %</b>	<b>37</b>	<b>36</b>	<b>27</b>	<b>36</b>	<b>54</b>	<b>0.075</b>
<b>Statin, %</b>	<b>41</b>	<b>57</b>	<b>44</b>	<b>21</b>	<b>42</b>	<b>0.462</b>
<b>Data are mean ± SD or percentage.</b>						
<b>MI, myocardial infarction; PCI, percutaneous coronary intervention;</b>						
<b>Hb, hemoglobin; UA, uric acid; LDL-C, low-density lipoprotein cholesterol;</b>						
<b>HDL-C, high-density lipoprotein cholesterol;</b>						
<b>BNP, brain natriuretic peptide; ADA, antidiabetic agents; ATA, antithrombotic agents;</b>						
<b>CCB, calcium-channel blocker; RAS-I, renin-angiotensin system inhibitor.</b>						

Table 2  
Hemodynamic and SPECT data

	Group					p Value
	Total	A	A + 25W	A + 35W	A + 45W	
Hemodynamic parameters						
SBP pre, mmHg	144 ± 20	144 ± 21	148 ± 18	137 ± 22	148 ± 21	0.182
post, mmHg	178 ± 41	146 ± 26	187 ± 39	175 ± 40	202 ± 37	< 0.001
DBP pre, mmHg	76 ± 15	74 ± 15	77 ± 13	74 ± 16	80 ± 16	0.387
post, mmHg	80 ± 28	69 ± 19	77 ± 18	80 ± 38	95 ± 30	0.013
HR pre, bpm	76 ± 13	76 ± 12	75 ± 12	76 ± 17	78 ± 10	0.905
post, bpm	105 ± 22	80 ± 12	107 ± 18	105 ± 17	124 ± 17	< 0.001
RPP pre	10,902 ± 2282	10,854 ± 2236	11,054 ± 2296	10,266 ± 2260	11,476 ± 2241	0.28
post	19,109 ± 6880	11,690 ± 2916	20,089 ± 5625	18,377 ± 4741	25,685 ± 6467	< 0.001
delta	8207 ± 6250	836 ± 2265	9035 ± 4769	8111 ± 3554	14,209 ± 6173	< 0.001
SPECT data						
EDV stress, mL	67 ± 23	64 ± 24	72 ± 26	66 ± 23	65 ± 16	0.505
rest, mL	68 ± 23	65 ± 24	71 ± 26	68 ± 23	66 ± 18	0.721
ESV stress, mL	21 ± 13	21 ± 12	24 ± 16	21 ± 11	18 ± 9	0.46
rest, mL	20 ± 13	20 ± 12	20 ± 13	20 ± 11	17 ± 9	0.672
EF stress, %	70 ± 10	68 ± 11	70 ± 12	69 ± 8	73 ± 7	0.286
rest, %	73 ± 9	71 ± 9	73 ± 9	72 ± 9	76 ± 8	0.286
SSS	1.3 ± 1.2	1.0 ± 1.2	1.2 ± 1.1	1.6 ± 1.1	1.4 ± 1.2	0.345
SRS	1.3 ± 1.6	1.0 ± 21.9	1.1 ± 1.3	2 ± 1.7	1.1 ± 1.2	0.06
SDS	0.7 ± 0.9	0.7 ± 1.1	0.7 ± 0.8	0.6 ± 0.6	0.9 ± 1.1	0.685
Data are mean ± SD.						

Group
SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate;
RPP, rate pressure product; EDV, end-diastolic volume; ESV, end-systolic volume;
EF, ejection fraction; SSS, summed stress score; SRS, summed rest score;
SDS, summed difference score.

In all the patients, the logarithmic values of  $H/L$  and  $H$ /below the  $H$  ratios positively correlated with heart rate ( $p = 0.004$  and  $p = 0.008$ , respectively), rate pressure product (RPP;  $p = 0.005$  and  $p = 0.008$ , respectively), and the increment of RPP (delta RPP;  $p = 0.002$  and  $p = 0.005$ , respectively) after stress in the univariate analysis (Table 3). The LVEDV after stress ( $p = 0.002$ ) negatively correlated with the logarithmic value of  $H$ /below the  $H$  ratio, but not  $H/L$  ratio. Although male sex was independently associated with the logarithmic values of both  $H/L$  ratio ( $p = 0.014$ ) and  $H$ /below the  $H$  ratio ( $p = 0.001$ ) in the multivariate regression analysis, LVEDV was also independently associated with the logarithmic value of  $H$ /below the  $H$  ratio ( $p < 0.001$ ; Table 3).

Table 3  
Correlation with heart-to-background activity ratio

	<b>Univariate</b>	<b>Multivariate</b>		
	<b>p Value</b>	<b>p Value</b>	<b>Coefficient</b>	<b>95% Confidence interval</b>
<b>log (H/L ratio)</b>				
<b>Age</b>	0.752	0.413	<b>0.0011</b>	<b>-0.0015 ~ 0.0037</b>
<b>Male</b>	0.040	0.014	<b>0.0631</b>	<b>0.0126 ~ 0.1135</b>
<b>HR post</b>	0.004	0.176	<b>0.0013</b>	<b>-0.0006 ~ 0.0032</b>
<b>RPP post</b>	0.005	0.329	<b>-0.0001</b>	<b>-0.0001 ~ 0.0001</b>
<b>Delta RPP</b>	0.002	0.124	<b>0.0001</b>	<b>-0.0001 ~ 0.0001</b>
<b>log (H/below the H ratio)</b>				
<b>Age</b>	0.773	0.981	<b>-0.0001</b>	<b>-0.0020 ~ 0.0020</b>
<b>Male</b>	0.188	0.001	<b>0.0683</b>	<b>0.0272 ~ 0.1094</b>
<b>HR post</b>	0.001	0.185	<b>0.0009</b>	<b>-0.0004 ~ 0.0024</b>
<b>RPP post</b>	0.008	0.278	<b>-0.0001</b>	<b>-0.0001 ~ 0.0001</b>
<b>delta RPP</b>	0.005	0.124	<b>-0.0001</b>	<b>-0.0001 ~ 0.0001</b>
<b>EDVex</b>	0.002	< 0.001	<b>-0.0017</b>	<b>-0.0027 ~ -0.0008</b>
H/L, heart-to-liver activity ratio; H/below the H, heart-to-below the heart;				
HR, heart rate; RPP, rate pressure product;				
EDVex, end-diastolic volume after exercise				

No significant side effects except for mild nausea and hypotension attributable to the ATP infusion in combination with exercise were observed, and our protocol was well tolerated in this study.

## Discussion

In this study, we enrolled only patients whose SSSs were < 3 to perform a robust and accurate evaluation of artifacts. The main finding of our study was that concomitant 6-min low-grade exercise supplementation with  $\geq 35$  W, through the use of the bicycle protocol, increased heart-to-background count ratios such as *H/L* and *H/below the H* ratios in the patients who underwent ATP stress MPI. The other findings of this study were that in the case of the *H/below the H* ratio, the artifact was independently associated with the LVEDV after exercise. The differences in the hemodynamic parameters such as RPP were not important factors for the evaluation of artefactual grade.

Side effects are common during standard adenosine stress testing. However, few significant side effects attributable to the ATP infusion in combination with exercise were observed, and this procedure was well tolerated in this study. Exercise increases the sympathetic nerve activity, which improves atrioventricular conduction and suppresses the vasodilation of adenosine in diaphragmatic lesions [10]. Pannell et al. [3] reported significant reductions in noncardiac side effects and major arrhythmias in combination with semi-spine bicycle exercise and adenosine stress. Furthermore, they found that the heart-to-background count ratio was higher in the exercise groups and correlated with the exercise level achieved. Samady et al. found that a 6-min adenosine infusion with concomitant low-level treadmill exercise reduced unfavorable side effects, enhanced image quality, and may have resulted in greater detection of ischemia [11]. Enhancement of image quality was observed when the adenosine infusion study was performed as compared with the bicycle-exercise protocol in patients treated with beta-blockade [12]. However, the opposite results were reported by Jamil et al., who showed no change in defect size or severity compared with the standard 6-min adenosine infusion [13].

A clear increase in  $H/L$  ratio is an important finding because an increased  $H/L$  ratio has been shown to result in fewer artifacts in the inferior and inferoseptal regions of the heart [1, 2]. In our study, we included only patients whose SSSs were  $< 3$  to evaluate precisely the extent of background level. When combined with ATP plus short-duration exercise stress, mild stress was adequate to obtain a significant quality image. Some differences were found between the results in the two regions regarding the quantification of the target-to-background ratio. The  $H$ /below the  $H$  ratio represents a comparison of the image quality of the heart with those of organs adjacent to the heart, such as the diaphragm, intestine, and other digestive tissues, and was inversely dependent on LVEDV in association with male sex. Enlargement of the left ventricle may reduce the sharpness of the SPECT image because of the increase in the dispersion of  $^{99m}\text{Tc}$  tetrofosmin in case of  $H$ /below the  $H$  ratio. By contrast, only male sex, irrespective of left ventricular size, was an independent factor for  $H/L$  ratio. Sex-related differences in artifacts may result from the grade of fat tissue and complicated body structures, including the lung, spine, and chest wall. A pertinent question that should be answered in the future is how a higher image quality can be obtained in patients with enlarged left ventricles when the use of a new type of stress method is becoming widespread in myocardial perfusion SPECT.

A considerable interpatient variability exists in the heart-to-background count ratios, but some extent of the exercise level achieved greater heart-to-background count ratio, which did not depend on the extent of the RPP. A short-duration exercise stress of  $\geq 35$  W may enhance sympathetic activity abruptly and adequately, thus leading to the desirable results. Improvement of the heart-to-background count ratio was present at the lower exercise levels, which most patients could be expected to achieve. Six-min ATP infusion with a moderately low-grade exercise protocol during the same period is preferable because it can be incorporated into the standard drug stress regimen with no time loss.

## Limitations

Depending on the protocol design, the type of tracer, moment of tracer injection, and type and duration of exercise may vary [14–18] and elicit different results. Whether these issues have any effects on the accuracy of the perfusion study are currently unclear. We could not use SPECT-computed tomography scanner to reduce artifacts in our study. As we randomly assigned patients into four groups but enrolled only those with SSSs of < 3, the number of patients differed among the groups. Under this condition, the defect severity and sensitivity to coronary artery disease in each group could not be evaluated.

## Conclusion

ATP administration concomitant with mild exercise stress of  $\geq 35$  W was useful for reducing undesired artifacts evaluated on the basis of heart-to-background ratio, irrespective of the extent of the RPP.  $H/L$  ratio was associated with male sex, while  $H$ /below the  $H$  ratio was associated with the LVEDV after stress in addition to male sex. The factors that cause artifacts might be different between target organs.

## Abbreviations

ATP, Adenosine triphosphate; H, heart; L, liver; LVEDV, left ventricular end-diastolic volume; MPI, myocardial perfusion imaging; RPP, rate pressure product; SPECT, single-photon emission computed tomography; SSS, summed stress scores.

## Declarations

### *Ethics approval and consent to participate*

This study complied with the tenets of the Declaration of Helsinki, and the protocol was approved by the ethics committee of our hospital (Ethics Committee of Yao Municipal Hospital). All patients provided written informed consent to participate.

### *Consent for publication*

All authors have read and approved the submission of the manuscript.

### *Availability of data and material*

The data and material in this manuscript are available (attached file).

### *Competing interests*

The authors have no financial or other relations that could lead to a conflict of interest.

### *Funding*

None.

### *Authors' contributions*

(1) conception and design of the study, or acquisition of, or analysis and interpretation of data: YS, TM, HF, HI, KU, SI, KM, KU.

(2) drafting the article or revising it critically for important intellectual content: YS, TK, SH.

(3) final approval of the version to be submitted: All authors have read and approved the submission of the manuscript.

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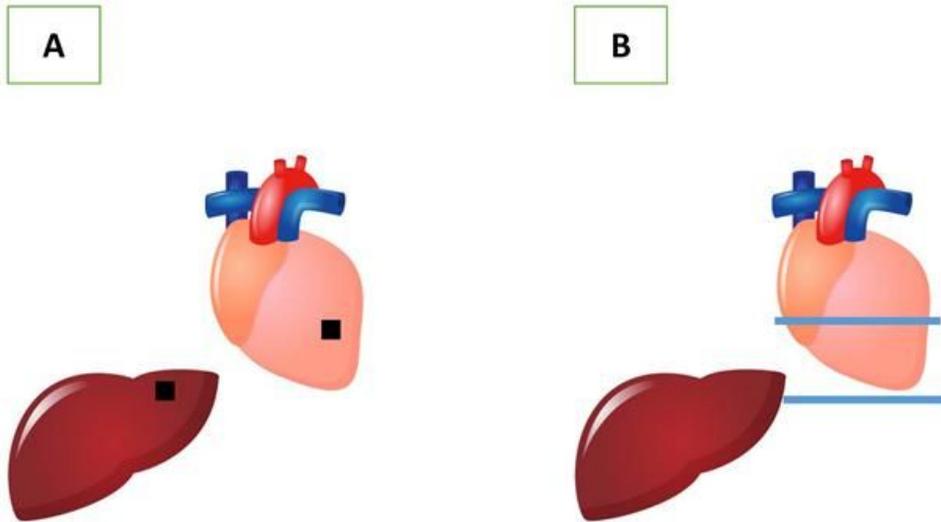
None.

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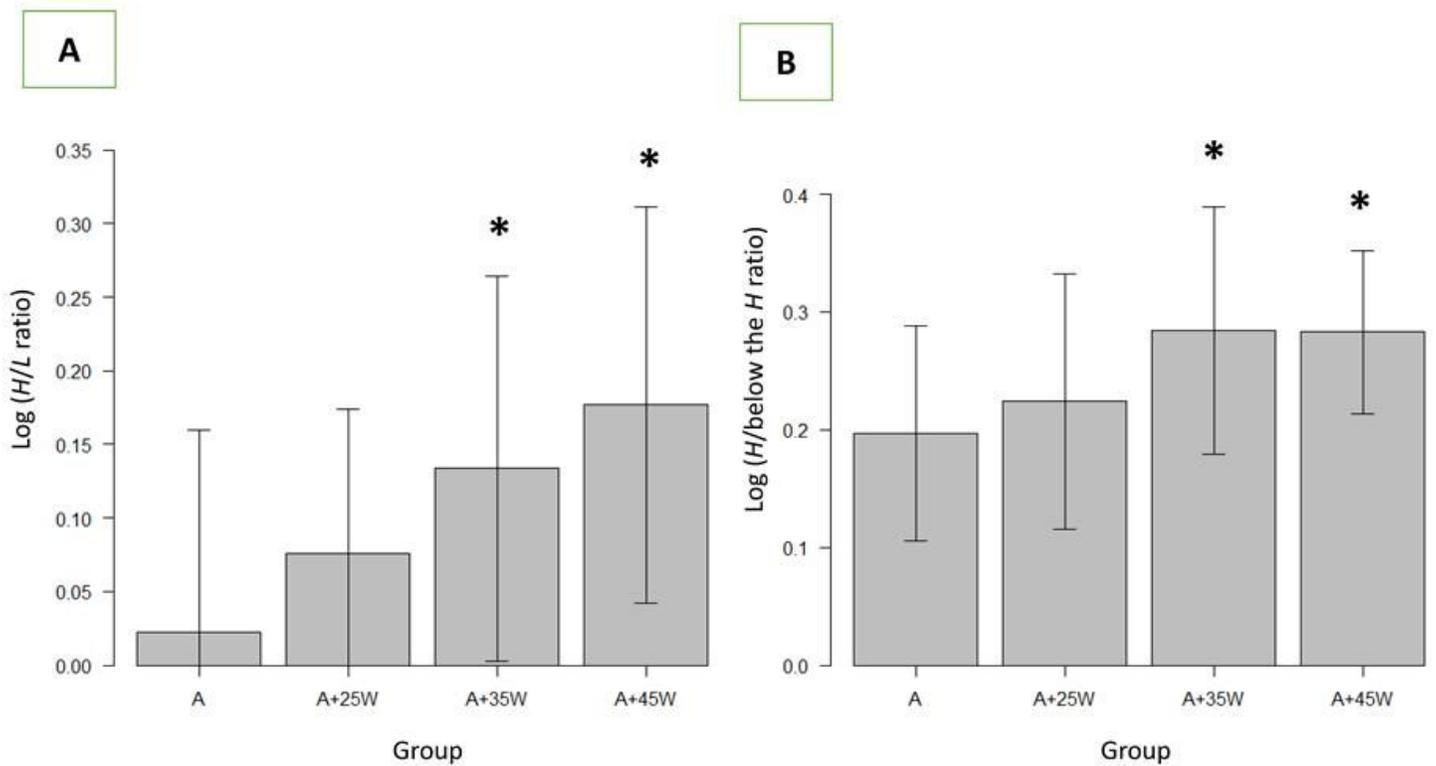
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## Figures



**Figure 1**

(a) Heart-to-liver (H/L) ratio: The regions of interest are drawn around the heart and liver, excluding the gall bladder. "Heart counts" and "liver counts" were obtained from the point of the maximum counts in each region of interest. (b) Heart-to-below the heart (H/below the H) ratio: The profile lines are placed on the heart and below the heart from the bottom of heart image to 10 pixels. "Heart counts" were obtained from the maximum count in the profile line, and "below the heart counts" were obtained from the minimum count in the profile line.



**Figure 2**

Differences in the logarithmic values of the heart-to-liver activity (H/L) ratio (a) and heart-to-below the heart activity (H/below the H) ratio (b) among the four groups (mean  $\pm$  SD). The values calculated using the post hoc Bonferroni test in groups A+35 W and A+45 W were significantly different compared with those in group A. \* $p < 0.05$ , compared with group A.

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