Serum High-sensitivity C-reactive Protein Level and Corrected QT Interval in Agricultural Workers in Myanmar Exposed to Chronic Occupational Organophosphate Pesticides

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Abstract: Although acute organophosphate (OP) pesticide poisoning is associated with the risk of cardiovascular diseases (CVD), the association between chronic occupational OP pesticide exposure and CVD risk is limited. We investigated serum high-sensitivity C-reactive protein (hs-CRP) levels and QTc intervals in 45 agricultural workers who were chronically exposed to OP pesticides and 45 non-exposed subjects. Serum hs-CRP level was determined by enzyme-linked immunosorbent assay (ELISA) and a level >1.0 mg/l was regarded as CVD risk. The QT interval was measured by routine 12-lead Electrocardiogram (ECG) with Lead II rhythm, and QTc was calculated. The median value of the serum hs-CRP level [1.20 (0.67–2.38) vs 0.74 (0.41–1.17) mg/l, \( P < 0.05 \)] and the mean QTc interval [422.71 ± 23.73 vs 396.27 ± 18.48 ms, \( P < 0.0001 \)] was significantly higher in the OP pesticide exposed subjects. Pesticide exposure was significantly associated with CVD risk (Chi-Square \( \chi^2 = 6.480, P = 0.011 \)) and QTc interval prolongation (\( \chi^2 = 13.846, P < 0.001 \)). A higher risk of CVD (odds ratio = 3.030; 95% confidence interval = 1.276 – 7.197) was observed in the OP pesticide exposed subjects. This study suggested that OP pesticide exposure should be considered as one of the significant risk factors for CVDs.

Keywords: high-sensitivity C-reactive protein, corrected QT interval, organophosphate pesticides, erythrocyte acetylcholinesterase enzyme activity, agricultural workers.

(Received November 16, 2020, accepted January 22, 2021)
the postmortem heart after OP pesticide poisoning [13, 16, 17]. Likewise, as an inflammatory marker, serum C-reactive protein (CRP) level was observed to have increased significantly in pesticide exposed subjects [18–20]. Available evidence indicates that chronic low-grade inflammation is involved in the pathogenesis of CVDs [21, 22]. The highly sensitive C-reactive protein (hs-CRP), which accurately detects low levels of CRP, enables a measure of persistent low grade systemic inflammation, and thus has been added to the risk factors for CVDs. The cut-off points of hs-CRP level are set as <1.0 mg/l, 1.0–3.0 mg/l, and >3.0 mg/l for low, average and high cardiovascular risk groups, respectively [23, 24]. The prolonged corrected QT interval is the most common and most important electrocardiographic abnormality, leading to sudden cardiac death in acute OP pesticide poisoning [25–28]. According to the results of an animal experiment, a lethal dose of the OP nerve agents sarin and soman inhibit the Ito potassium current and the Na⁺/Ca²⁺ exchanger, which delay the ventricular repolarization phase and subsequently prolong the QTc interval [14]. According to the Bazett formula (QTc = QT/square root of RR interval) [29], the QTc is considered prolonged when it is longer than 440 ms [30, 31]. Prolonged QTc interval is a strong predictor of incident cardiovascular morbidity and mortality, independent of other risk factors [32, 33].

Most previous studies assessed the degree of occupational OP pesticide exposure by self-reported histories of lifetime pesticide use and current farm activities, percentage of country’s land area dedicated to farming, and clinical effects of OP pesticide poisoning. Since OP pesticides are known to be specific inhibitors of acetylcholinesterase (AChE) enzyme activity [34, 35], the present study assessed the level of AChE inhibition to confirm pesticide exposure, and investigated the cardiovascular risk by measuring serum hs-CRP levels and QTc intervals in agricultural workers chronically exposed to occupational OP pesticides in Mingalardon Township, Yangon, Myanmar. Myanmar being an agricultural country, most agricultural workers are inevitably exposed to pesticides and use them without much awareness of side effects. This study also intends to raise public awareness of the harmful effects of OP pesticides on the cardiovascular system in agricultural workers.

**Materials and Methods**

**Recruitment of participants**

This cross-sectional study was undertaken in apparently healthy adult male subjects, aged 20–40 years, residing in Mingalardon Township, Yangon. We excluded subjects with a history of chronic infection, connective tissue diseases, malignancies, known history of hypertension, diabetes mellitus, heart disease, renal diseases, liver diseases, heavy alcohol drinkers, heavy smokers, and those taking drugs within 2 weeks that are likely to affect serum hs-CRP level and QT interval. Other conditions associated with reduced AChE enzyme activity, such as hemolytic anemia, heavy alcohol drinking and heavy metal exposure, were also considered as exclusion criteria in the present study. Those with resting blood pressure (BP) >140/90 mmHg and those with body mass index (BMI) outside the range of 18.5 to 24.9 kg/m² were excluded from the study. Fasting blood sugar (FBS) level was determined by using a glucometer, and subjects with FBS >126 mg/dl were excluded from the study.

We collected 3 ml of blood from the subjects in ethylenediamine tetra acetic acid (EDTA) tubes for packed cell separation. All the blood samples were transported to the Common research laboratory, University of Medicine 2, Yangon, with an effective cold chain system. On arrival, the blood in the EDTA tube was centrifuged at 1,000 rpm for 15 minutes. The supernatant plasma anduffy coat were removed and the packed cells were washed three times with isotonic saline. Erythrocyte AChE enzyme activity was determined by using the spectrophotometric Ellman method [36], on the same day of blood collection.

When OP pesticides enter the body through contact with the mucous membrane, inhalation or ingestion, they avidly bind to the oxygen of the serine hydroxyl group located at the active site of AChE enzyme, leading to inhibition of this enzyme activity [37]. Thus, decreased AChE enzyme activity is an indicator of chronic OP pesticide exposure. Non-agricultural workers could be indirectly exposed to OP pesticides by means of inhalation and ingestion if they go, for other purposes, around farms that use pesticides or if they eat food and water contaminated with OP pesticides. Hence, the present study recruited individuals with AChE enzyme
activity more than 5,950 U/l (no inhibition of enzyme activity) as the OP pesticide non-exposed subjects [35]. Individuals who had a history of OP pesticide exposure for at least 5 years were selected as OP pesticide exposed subjects. From each group, 45 subjects were recruited to this study by consecutive sampling according to sample size calculation and determination. Participation in the research was absolutely voluntary.

**Questionnaire Application**

Information was collected through in-person interviews and included personal identification (completed age in year, address), history of heavy smoking (20 or more cigarettes or cheroots per day for at least one year), history of heavy alcohol drinking (more than 3 units of alcohol per day), occupational history, past medical history (chronic disorders of the joints, acute and chronic infection, connective tissue diseases, malignancy, hypertension, diabetes mellitus, heart disease, renal diseases, liver diseases), history of taking medicine (including traditional medicine), history of agricultural work (duration of exposure; frequency of pesticide use per week; last date of pesticide exposure; type of pesticides, used such as trade names and active ingredients; personal protective measures, such as hand gloves, eye protection, facial mask, boots and body protection; precautions taken after pesticide application, such as washing the hands, clothes and body; site of pesticide preparation; and storage of pesticides, such as inside home or inside compound).

**Active Compounds in Pesticides**

Among the brands of commercially distributed agricultural pesticides in Myanmar, Aw-Ba and Wi-Sar-Ra are composed mainly of OP compounds (about 75%) and are commonly used in; study area (Table 1). Other alternative brands were also reported as being used.

**Table 1. Active compounds in pesticides commonly used in Mingalardon Township, Yangon, Myanmar**

| Brand Name | Items | Active compounds                                           |
|------------|-------|------------------------------------------------------------|
| Aw-Ba      |       |                                                            |
| Byter Nan Chat Ku 3.2 ME | Cybermethrin 3.0% + Emamectin benzoate 0.2% |
| ShweMida 70 WP | Copper Hydroxide 77% |
| Copxide 77 WP | Carbofuran 3% |
| Carbofuran 3G | Terbufos 10% GR |
| Hunter     |       |                                                            |
| Better 25 WP | Acetamiprid 20% + Lambda-cyhalothrin 5% |
| Demon 1.8 EC | Abamectin 1.8% |
| Abatin 1.8% EC | Abamectin 1.8% EC |
| Curadrin 50 EC | Profenofos 50% |
| LAUN-25 WP |       |                                                            |
| CARBEN 50 SC | Metalaxyl 25% |
| ALARM 15 WP |       |                                                            |
| Cyclone 505 EC | Chlorpyrifos 45.90% w/w + Cypermethrin 4.59% w/w |
| Azphate 75 SP | Acephate 75% SP |
| Azphate II 80 SP | Acephate 77.5% + Lambda-cyhalothrin 2.5% EC |
| DOZER 20 WP |       |                                                            |
| DOZER 70 WP | Imidacloprid 70% |
| Wi-Sar-Ra  |       |                                                            |
| Ready 505 EC | Chlorpyrifos 50% + Cypermethrin 5% |
| S-PHATE 75 SP | Acephate 75% w/w |
| Zero       |       | Paraquat dichloride 27.6% SL                               |
| GLYPHAUK 480 SL | Glyphosate 480 g/l (41.2% w/w) |
| Landa 2.5 EC | Lambda-cyhalothrin 2.5% EC                                |
| Landa 5 EC  | Lambda-cyhalothrin 5% EC                                  |
**Sample Collection**

A routine 12-lead ECG (25 mm/s paper speed and 10 mm/mV amplitude) and lead II rhythm strip for 10 seconds were taken after a supine resting period of at least 15 min by using an ECG machine (ECG-300G, Contact Medical Systems Co., Ltd, China). About 3 ml of venous blood sample was collected in plain tubes under aseptic conditions. All the blood samples were transported to the Common research laboratory, University of Medicine 2, Yangon with an effective cold chain system. On arrival, serum/plasma separation was done by centrifuging at 2,000 rpm for 10 minutes and stored at -20°C until sample analysis.

This study was approved by the Ethics and Research Committee of the University of Medicine 2, Yangon. On every visit, safe handling procedures for pesticide application and storage were explained to agricultural workers. Immediate first aid assistance was also prepared to be provided to any person with signs and symptoms of pesticide poisoning.

**Data Analysis**

The QT interval was measured from the start of the Q wave to the end T wave in a normal beat. The RR is the time interval between two consecutive R waves, measured in seconds. Heart rate was calculated from average RR intervals of the beat within 10 seconds. The QT interval and RR interval were measured by using Vernier Caliper, and the corrected QT interval (QTc) was calculated by using Bazett’s formula [29];

\[ QTc \text{ (ms)} = \frac{QT \text{ (ms)}}{\sqrt{RR(s)}} \]

The QTc is considered prolonged when it is longer than 440 ms [30, 31].

Analysis of serum hs-CRP level was done by using the ELISA kit (EIA-3954, DRG International Inc., USA). Risk groups of CVDs have been defined by the cut-off points of hs-CRP level as <1.0 mg/l (low risk), and >1.0 mg/l (high risk).

**Statistics**

Data entry and analysis were done by SPSS software (Statistical Package for Social Sciences) version 16.0. Normally distributed variables were expressed as mean ± SD and comparison was done by using the independent ‘t’ test. Skewed data was expressed as median (interquartile range, IQR) and computed by the non-parametric Mann-Whitney U test. Pearson’s Chi-Square test was used to find out the association between two variables. The odds ratio was calculated for the estimation of risk. For correlation, Pearson’s (r) was used for normally distributed data, and Spearman’s rho (ρ) was used for skewed data. Differences were considered significant when \( P < 0.05 \).

**Results**

**Participants’ characteristics**

The general characteristics of the subjects who participated in the present study are shown in Table 2. The factors which are likely to affect the serum hs-CRP level and QTc interval were adjusted. Hence, there were no significant differences in BMI, systolic BP, diastolic BP, heart rate and FBS, but the mean value of age in the OP pesticide exposed group was significantly higher than that in the non-exposed group. Although age is

| Parameters          | non-exposed group (mean ± SD) (n = 45) | OP pesticide exposed group (mean ± SD) (n = 45) | P-value |
|---------------------|----------------------------------------|-----------------------------------------------|---------|
| Age (years)         | 27.62 ± 5.69                           | 31.24 ± 5.82                                  | 0.004   |
| Height (m)          | 1.62 ± 0.05                            | 1.62 ± 0.05                                   | 0.938   |
| Weight (kg)         | 56.40 ± 7.12                           | 56.16 ± 7.69                                  | 0.876   |
| BMI (kg/ m²)        | 21.39 ± 2.19                           | 21.22 ± 2.33                                  | 0.724   |
| SBP (mmHg)          | 117.11 ± 9.68                          | 116.89 ± 9.25                                 | 0.912   |
| DBP (mmHg)          | 76.44 ± 6.45                           | 78.44 ± 6.38                                  | 0.143   |
| Heart rate (beats/min) | 75.56 ± 9.97                           | 76.71 ± 12.34                                 | 0.626   |
| FBS (mg/dl)         | 100.18 ± 5.74                          | 98.40 ± 7.58                                  | 0.213   |

Significant difference was considered when \( P < 0.05 \), OP: organophosphate, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBS: fasting blood sugar.
considered a risk factor for CVD, it was negligible in the 20-to-40-year-old subjects in the present study because the age-related change of CVD risk was observed especially in age over 40 years [38].

Analysis of serum hs-CRP level

The median (IQR) values of serum hs-CRP level were 1.20 (0.67–2.38) mg/l in the agricultural workers exposed to OP pesticides and 0.74 (0.41–1.17) mg/l in the non-exposed group. It was significantly higher in the OP pesticide exposed group than in the non-exposed group ($P<0.05$) (Figure 1). A significant association was found between OP pesticide exposure and serum hs-CRP level >1.0 mg/l (Pearson’s Chi-Square $\chi^2 = 6.480, P = 0.011$) (Table 3). It was also observed that the hs-CRP cut-off point >1.0 mg/l for high-risk of future cardiovascular event was 3.03 times more common in the OP pesticide exposed group than in the non-exposed group (OR = 3.030, 95% CI = 1.276–7.197).

Analysis of QTc interval

The mean QTc interval in the agricultural workers exposed to OP pesticides (422.71 ± 23.73 ms) was significantly more prolonged than that in the non-exposed group (396.27 ± 18.48 ms) ($P<0.0001$) (Figure 2). A significant association was found between OP pesticide exposure and prolonged QTc interval (Pearson’s Chi-Square $\chi^2 = 13.846, P<0.001$) (Table 4).

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**Table 3. Association between organophosphate pesticide exposure and serum high-sensitivity C-reactive protein level**

| Subjects with          | OP pesticide exposed group (n = 45) | Non-exposed group (n = 45) | *$P$-value |
|------------------------|------------------------------------|---------------------------|------------|
| Serum hs-CRP level $>$1.0 mg/l (n%) | 26 (57.8%)                         | 14 (31.1%)                | 0.011      |
| Serum hs-CRP level $<$1.0 mg/l (n%) | 19 (42.2%)                         | 31 (68.9%)                |            |

*Pearson’s Chi-Square test. Serum hs-CRP level $>$1.0 mg/l, high CVD risk; Serum hs-CRP level $<$1.0 mg/l, low CVD risk. OP: organophosphate, hs-CRP: high-sensitivity C-reactive protein, CVD: cardiovascular diseases.
Correlation between erythrocyte AChE enzyme activity and serum high-sensitivity C-reactive protein level and QTc interval

Significant weak negative correlations were observed between erythrocyte AChE enzyme activity and serum hs-CRP level (Spearman’s rho $\rho = -0.301$, $P < 0.05$, n = 90) (Figure 3) as well as QTc interval (Pearson’s $r = -0.405$, $P < 0.0001$, n = 90) (Figure 4) in the whole study population.

**Discussion**

All 45 of the agricultural workers had erythrocyte AChE enzyme activity less than 5,950 U/l. Only 45 subjects (36.5%) out of 123 non-agricultural workers met the inclusion criteria of non-exposed group with erythrocyte AChE enzyme activity more than 5,950 U/l [35], and the remaining 78 subjects were excluded from the study. The present study also noted that 78 (63.5%) out of 123 non-agricultural workers had erythrocyte AChE enzyme activity less than 5,950 U/l even though they did not have a history of OP pesticide exposure in their lives. It can be assumed that pesticides might enter the body by eating food and drinking water contaminated with pesticides since many pesticides are not easily degradable and they persist in vegetable crops, soil, ground and surface water. The present study excluded the signs and symptoms of anemia and heavy metal toxicity (diarrhea, vomiting, abdominal cramps, shortness of breath, etc.), and history of heavy alcohol drinking which would affect AChE enzyme activity, though an investigation of the status of anemia and heavy metal contamination in food and water was not done.

It was also observed that the mean value of erythro-

**Table 4. Association between organophosphate pesticide exposure and prolonged corrected QT interval**

|                      | OP pesticide exposed group (n = 45) | Non-exposed group (n = 45) | *P*-value |
|----------------------|-----------------------------------|---------------------------|-----------|
| Subjects with       |                                    |                           |           |
| Prolonged QTc (>440 ms) (n%) | 12 (26.7%)                        | 0 (0%)                    | <0.001    |
| Normal QTc (<440 ms) (n%)    | 33 (73.3%)                        | 45 (100%)                 | ($\chi^2 = 13.846$) |

*Pearson’s Chi-Square test. OP: organophosphate.
cyte AChE enzyme activity in the non-exposed group was 6,393.36 ± 295.38 U/l (range from 5,956 to 7,286 U/l) and that in the OP pesticide exposed group was 4,845.95 ± 665.07 U/l (range from 2,869 to 5,819 U/l). Inhibition of AChE enzyme activity was classified as high (≤3,950 U/l), mild (3,950 to ≤5,950 U/l) or no inhibition (>5,950 U/l), based on a study by Ohayo-Mitoko et al [35]. Accordingly, 5 out of 45 agricultural workers in the present study had high AChE enzyme inhibition and the remaining 40 had mild inhibition. The mean duration of OP pesticide exposure for agricultural workers was 9.18 ± 2.99 years, and they are still engaged in agriculture. At the time of sample collection, the most commonly used pesticide brands in the Mingalardon region were Aw-Ba and Wi-Sar-Ra, which are mainly composed of OP compounds (Table 1). Thus, the agricultural workers who participated in the present study were found to be in a state of chronic low-level OP pesticide exposure. Moreover, the majority of agricultural workers in the present study were found to be unaware of the harmful effects of pesticides through poor handling, storage, and application, and they did not follow the post-application steps such as washing the contaminated hands and clothes.

The present study also showed a significant increase of mean serum hs-CRP level in the OP pesticide exposed group compared the non-exposed group (P < 0.05). This finding was consistent with the results of previous studies [18–20]. Moreover, the hs-CRP cut-off point >1.0 mg/l for high-risk of future cardiovascular event was 3.03 times more common in the OP pesticide exposed subjects than in the non-exposed subjects (OR = 3.030, 95% CI = 1.276–7.197). The present study also showed that erythrocyte AChE enzyme activity was significantly and weak negatively correlated with serum hs-CRP level in the whole study population (Spearmann’s rho ρ = −0.301; P < 0.05; n = 90).

There have been documented links of pesticide exposure with various inflammatory responses. According to Ahmad and Dogar, pesticides frequently produce reactive oxygen species which cause cellular and tissue damage [10]. As a consequence, the Nuclear factor-kappa B (NF-kB), a transcription factor essential for inflammatory responses, gets activated and produces a large amount of proinflammatory cytokines, especially IL-6, which then stimulate the liver to up-regulate the production of a large amount of acute phase proteins, CRP. In a histopathological study done by Velmurugan et al, nonspecific inflammatory changes of cardiac muscle fibers were observed in OP pesticide-induced Wistar rats [13]. Similarly, gross and microscopic examination of postmortem heart of patients with OP pesticide poisoning showed pericarditis, myocarditis, myocardial interstitial edema and vascular congestion [16, 17].

Consistent with previous studies, the present study showed that the mean QTc interval in agricultural workers exposed to OP pesticides was significantly longer than that in the non-exposed group [25–27, 39–41]. However, most of these previous studies were conducted in patients with signs and symptoms of acute or severe OP pesticide poisoning, whereas the present study was undertaken in chronic OP pesticide exposed subjects without acute or severe signs and symptoms of OP toxicity. Moreover, even after excluding the subjects with high inhibition of AChE enzyme activity (n = 5), a significant difference in QTc interval was still present in the OP pesticide exposed subjects with mild inhibition of AChE enzyme activity (n = 40) compared with the non-exposed subjects. Accordingly, the present study concluded that a significant difference in QTc interval was also observed in agricultural workers with chronic low-level OP pesticide exposure.

Similar to the finding of a previous study done by Baydin et al [42], the current study showed a significant weak negative correlation between erythrocyte AChE enzyme activity and QTc interval in the whole study population (Pearson’s r = −0.405; P < 0.0001; n = 90). A significant association was also found between prolonged QTc interval (>440 ms) and OP pesticide exposure (Pearson’s Chi-Square χ² = 13.846, P < 0.001). As a result, it can be concluded that OP pesticide exposed subjects have a greater chance of CVD risk than that of non-exposed subjects, since QTc prolongation is associated with higher CVD morbidity and mortality independent of other risk factors [32, 33].

A possible mechanism for the prolongation of QTc in the OP pesticide exposed subjects in the present study might be persistent parasympathetic cholinergic overstimulation, which exerts an inhibitory action on the cardiac conduction system. The OP pesticides inhibit the AChE enzyme, leading to accumulation of
ACh and subsequent overstimulation of M1 muscarinic cholinergic receptors of cardiac ventricular myocyte, resulting in inhibition of potassium outward channels. As a consequence, an intracellular excess of positive ions delays ventricular repolarization and subsequently prolongs the QT interval. In an animal study, changes in ventricular electrical activity (I_{to}, I_{Kr}, I_{Ks} potassium currents and the Na⁺/Ca²⁺ exchanger) and subsequent prolongation of QT interval were observed in Sprague-Dawley albino rats after administration of the OP nerve agents sarin and soman [14]. Likewise, Zoltani and Baskin described in a computer study that organophosphate-modulated cardiac membrane currents (two potassium currents, I_{Kr}, I_{Ks}) generated a long QT syndrome [15]. All these studies take into account the concept of possible mechanisms between OP pesticide exposure and prolonged QTc interval.

As a cross-sectional observational study, the present study does not cover a large population and hence cannot clearly establish causality between pesticide exposure and CVD risk. Important confounders of decreasing the AChE enzyme activity, such as anemia and heavy metal exposure (arsenic, zinc, lead, etc.), that may affect the risk of CVD could not be investigated in the present study.

Conclusions

In conclusion, the findings of the present study provide evidence that chronic low-level exposure to OP pesticides has harmful effects on the cardiovascular system. It is an important public health concern, and we recommend that farm workers in Myanmar be provided awareness, knowledge and skills for safe use of pesticides.

Acknowledgments

This study was supported by grants from the Implementation Research Grant Committee, Ministry of Health and Sports, Myanmar (Project ID-028). We thank the Ethics review committee, University of Medicine 2, Yangon, the Republic of Myanmar for providing ethical clearance. We thank all the subjects who willingly participated in this research for their cooperation and patience.

Conflict of Interest

The authors declare no conflict of interest.

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