# Cardiovascular Topics

# Effect of heroin on right ventricular cardiac performance

Murat Selcuk, Ersin Yildirim, Faysal Saylik, Ozgur Deniz, Ferit Onur Mutluer

## Abstract

**Objective:** The aim of this study was to investigate the effects of heroin addiction, which is an important social and health problem, on right cardiac function.

**Methods:** A total of 85 individuals were included in the study. The study group comprised 45 patients smoking heroin and the control group was 40 healthy individuals with no drug addiction. Patients injecting heroin were excluded. Echocardiographic evaluation of patients using heroin was performed and compared with those in the control group.

**Results:** The right ventricle and pulmonary artery diameters in the heroin group were found to be higher compared to the control group. The myocardial performance index (MPI) was higher and more abnormal in the heroin group (0.48 ± 0.22 vs 0.39 ± 0.11, $p < 0.05$) whereas isovolumic acceleration (IVA) of the right ventricle was significantly lower in the heroin group (2.92 ± 0.69 vs 3.4 ± 0.68 m/s$^2$, $p < 0.01$). No significant difference was observed between the groups with regard to the right ventricular ejection fraction (RVEF) (59.6 ± 2.5 vs 60.6 ± 2.3%, $p = 0.08$), tricuspid annular plain systolic excursion (TAPSE) (24.1 ± 4.2 vs 24.5 ± 2.4 mm, $p = 0.7$), tissue Doppler imaging S wave (TDI-S) (13.7 ± 2.1 vs 13.8 ± 2.1 cm/s, $p = 0.86$) and right ventricular fractional area change (RVFAC) (42.7 ± 8.3 vs 43.9 ± 3.5%, $p = 0.4$). Multivariate and univariate regression analyses revealed independent correlation between the pulmonary artery diameter and RVIVA, and heroin addiction.

**Conclusion:** Heroin addiction negatively affected right ventricular function and more attention should be paid to the cardiac function of these patients.

**Keywords:** heroin, right ventricular function, myocardial performance index

**Department of Cardiology, Van Education and Research Hospital, University of Health Sciences, Van, Turkey**
Murat Selcuk, MD,
Faysal Saylik, MD
Ferit Onur Mutluer, MD

**Department of Cardiology, Istanbul Umraniye Education and Research Hospital, University of Health Sciences, Istanbul, Turkey**
Ersin Yildirim, MD, ersinyil44@gmail.com

**Department of Psychiatry, Van Education and Research Hospital, University of Health Sciences, Van, Turkey**
Ozgur Deniz, MD

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Heroin addiction is one of the most destructive and expensive public health problems. Heroin, which is a central nervous system depressant (diacetylmorphine), is a semi-synthetic opiate. Mortality rate among heroin users varies between 1 and 3%, and the most effective treatment method for heroin addiction is opioid replacement therapy.[1,2] Heroin is commonly smoked, snorted and injected intravenously.

A common negative effect of heroin addiction is respiratory depression, which may lead to death, especially following intravenous (IV) injection. Additionally, heroin-related pulmonary oedema has been reported in previous studies.[3] IV use of the drug is difficult to evaluate since the injection is generally performed together with other chemical substances named adulterants.[4]

Heroin addiction is a serious social health problem. We evaluated patients who smoked heroin and aimed to investigate its effect on right heart function since not much is known about the cardiac effect of heroin addiction.

## Methods

Informed consent was obtained from all patients and they signed a consent form to participate in the study. The Van Education and Research Hospital ethics committee approved the study.

A total of 85 individuals were included in the study. The study group comprised 45 patients smoking heroin and undergoing therapy in the Alcohol and Drug Addiction Treatment and Training Centre of the Van Training and Research Hospital between 2014 and 2016. The control group consisted of 40 healthy individuals with no drug addiction other than smoking cigarettes.

Subjects who used heroin via the IV route, alcoholics, those with coronary artery disease, cardiac failure, cardiac valve disorders, known arrhythmias, hypertension, congenital cardiac diseases, diabetes, hepatic or renal failure, chronic obstructive pulmonary disease, endocrine diseases, metabolic or electrolyte disorders, acute or chronic infections or those on medications due to any type of disease, were excluded from the study.

The clinical and demographic characteristics of the patients, and status and duration of heroin addiction were obtained from the patients and patient files in the hospital. Body mass index, defined as body mass divided by the square of the height, was determined. Electrocardiography (ECG) records of the patients were obtained via the Schiller Cardiovit AT-102 plus using the

standard 12 derivation (10 mm/mV calibration and 25 mm/s sliding rate). Complete blood counts and biochemical tests were performed using a Beckman Coulter LH-750 and Beckman Coulter L × 20, respectively, and the results of each patient were recorded.

Echocardiographic evaluations of the patients were performed at the time of admission to our hospital while the patients were still under the influence of heroin. All participants underwent two-dimensional (2D) and Doppler echocardiographic evaluation (VIVID 3, General Electric, USA). 2D echocardiographic studies were performed in the left lateral decubitus position with the conventional views (parasternal long- and short-axis, apical four-chamber views). Right ventricular ejection fraction (RVEF) from 2D methods was calculated as: (end-diastolic volume – end-systolic volume)/end-diastolic volume.

Right ventricular M-mode, tissue Doppler records, isovolumic acceleration (IVA) and myocardial performance index (MPI) measurements were performed for right ventricular systolic and diastolic function indicators. Peak myocardial speed during isovolumic contraction was defined as isovolumetric contraction velocity (IVV) (m/sec) and time elapsed to reach peak speed was defined as acceleration time (AT). IVA was calculated with the following formula: IVA = IVV/AT.

Right ventricular MPI was calculated as the ratio between the sum of the isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by the ejection time (ET): MPI = (ICT + IRT)/ET. Right ventricular fractional area change (RVFAC) was assessed in the four-chamber view and calculated as: RVFAC = [RV end-diastolic area – RV end-systolic area]/RV end-diastolic area × 100%. Pulsed tissue Doppler imaging (TDI) was performed to measure systolic and diastolic myocardial velocities at the basal level of the RV free wall. Peak myocardial IVV, peak myocardial systolic velocity (Sm), peak early and late diastolic velocities (Em and Am), ICT, IRT and ET were measured.

We used M-mode scanning to measure tricuspid annular plane systolic excursion (TAPSE) in the apical four-chamber view with the cursor placed at the free wall side of the tricuspid annulus to assess RV longitudinal function. TAPSE was measured as the distance between the peak and trough of the M-mode tracing curve, and at least three consecutive beats were averaged. All Doppler measurements were performed at the end of the expiration in order not to affect flow parameters with respiration and to be more consistent.

Averages of measurements were used for comparison. Measurements were generally consistent and this provided more stable results. Inter-observer agreement was evaluated by calculating the Pearson's correlation coefficient ($r = 0.93$).

## Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc, Chicago, IL) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium) programs. Compliance of the data to the normal distribution was tested using the Kolmogorov–Smirnov test. Normally distributed numeric variables are expressed as mean ± standard deviation and non-normally distributed variables are expressed as medians. Categorical variables are expressed as numbers and percentages.

For comparisons between the heroin and control groups, the Student's *t*-test was used for parametric variables and the Mann–Whitney *U*-test for non-parametric variables. The chi-squared and Fisher's exact chi-squared tests were carried out for comparison of categorical variables. Single-variate logistic regression analysis was performed in order to determine the effects of potential prognostic factors on right ventricular function. Significant risk factors were included in the multivariate logistic regression and independent predictors were determined. A *p*-value of $< 0.05$ was accepted as statistically significant.

## Results

In the heroin group, the mean duration of heroin use was 4.6 years. The mean red cell distribution width (RDW) in the heroin group was observed to be significantly higher compared to the control group (15 ± 1.6 vs 13.4 ± 1.1%, $p < 0.01$). No significant differences were found in other demographic and laboratory characteristics between the groups (Table 1).

Comparison of the echocardiographic characteristics between the groups revealed statistically larger right ventricular basal (39.4 ± 4.7 vs 35.6 ± 4.3 mm, $p < 0.01$), mid (37.2 ± 4.7 vs 31.8 ± 3.6 mm, $p < 0.01$) and apicobasal (60.8 ± 7.2 vs 53.6 ± 11.1 mm, $p = 0.01$) diameters and pulmonary artery diameter (22.4 ± 2.5 vs 20 ± 2.5 mm, $p < 0.01$) in the heroin group compared to the control group. Tricuspid pulsed wave E (PW E) (62.9 ± 14.8 vs 52.6 ± 12 cm/s, $p = 0.01$) and tissue Doppler e wave (17.2 ± 4.5 vs 14.3 ± 3 cm/s, $p = 0.01$) values in the heroin group were observed to be statistically higher compared to the control group. The MPI value was higher and abnormal in the heroin group (0.48 ± 0.22 vs 0.39 ± 0.11, $p < 0.05$), whereas the right IVA was observed to be significantly reduced in the heroin group (2.92 ± 0.69 vs 3.4 ± 0.68 m/s$^2$, $p < 0.01$). No significant differences were observed between the groups with regard to RVEF (59.6 ± 2.5 vs 60.6 ± 2.3%, $p = 0.08$), TAPSE (24.1 ± 4.2 vs 24.5 ± 2.4 mm, $p = 0.7$), TDI-S (13.7 ± 2.1 vs 13.8 ± 2.1 cm/s, $p = 0.86$) and RVFAC (42.7 ± 8.3 vs 43.9 ± 3.5%, $p = 0.4$) values (Table 2).

An independent correlation was observed between the RVIVA and heroin use in univariate [0.36 (0.18–0.72), $p < 0.01$] and multivariate [0.42 (0.19–0.88), $p = 0.02$] regression analyses.

**Table 1. Baseline characteristics and laboratory findings of the groups**

| *Variables* | *Heroin (+)* (n = *45*) | *Heroin (–)* (n = *40*) | p-*value* |
|---|---|---|---|
| Age (years), mean (SD) | 29.6 ± 9.6 | 30.1 ± 8.1 | 0.81 |
| Gender (female), *n* (%) | 2 (4.4) | 6 (15) | 0.09 |
| Diabetes mellitus, *n* (%) | 0 | 0 | – |
| Hypertension, *n* (%) | 0 | 0 | – |
| Coronary artery disease, *n* (%) | 0 | 0 | – |
| BMI, kg/m$^2$ | 26.5 ± 2.7 | 27.5 ± 2.7 | 0.11 |
| WBC (× 10$^3$ cells/µl) | 8.1 ± 1.7 | 7.9 ± 1.5 | 0.61 |
| Haemoglobin (g/dl) | 16.2 ± 0.9 | 15.7 ± 1 | 0.02 |
| RDW (%) | 15 ± 1.6 | 13.4 ± 1.1 | < 0.01 |
| Creatinine (mg/dl) | 0.84 ± 0.13 | 0.82 ± 0.1 | 0.31 |
| Platelet count (× 10$^3$ cells/µl) | 283.6 ± 80.5 | 279.6 ± 79.4 | 0.82 |
| Sodium (mmol/dl; SD) | 140.5 ± 3.4 | 140.8 ± 3.2 | 0.62 |
| Potasium (mmol/dl; SD) | 4.3 ± 0.38 | 4.32 ± 0.33 | 0.73 |
| Calcium (mg/dl; SD) | 9.2 ± 0.5 | 9.3 ± 0.4 | 0.84 |

$p < 0.05$ is statistically significant. Continues variables are reported as mean ± SD or median (IQR). Categorical variables are reported as *n* (%).
BMI: body mass ındex, WBC: white blood cells, RDW: red cell distribution width.

**Table 2. Echocardiographic features of the groups**

| *Variables* | *Heroin (+)* | *Heroin (–)* | p-*value* |
|---|---|---|---|
| RVEF (%) | 59.6 ± 2.5 | 60.6 ± 2.3 | 0.08 |
| Intraventricular septum (mm) | 8.7 ± 1.3 | 8.6 ± 0.9 | 0.79 |
| Right atrium area ($mm^2$) | 16.2 ± 2.9 | 14.9 ± 2.6 | 0.04 |
| RV basal diameter (mm) | 39.4 ± 4.7 | 35.6 ± 4.3 | < 0.01 |
| RV mid diameter (mm) | 37.2 ± 4.7 | 31.8 ± 3.6 | < 0.01 |
| RV apicobasal (mm) | 60.8 ± 7.2 | 53.6 ± 11.1 | 0.01 |
| Pulmonary artery diameter (mm) | 22.4 ± 2.5 | 20 ± 2.5 | < 0.01 |
| RV wall thickness (mm) | 4.7 ± 1.1 | 4.6 ± 1 | 0.81 |
| RVFAC (%) | 42.7 ± 8.3 | 43.9 ± 3.5 | 0.44 |
| TAPSE (mm) | 24.1 ± 4.2 | 24.5 ± 2.4 | 0.71 |
| Pulsed Doppler MPI | 0.48 ± 0.22 | 0.39 ± 0.11 | 0.02 |
| Tricuspid PW E (cm/s) | 62.9 ± 14.8 | 52.6 ± 12 | 0.01 |
| Tricuspid PW A (cm/s) | 44.1 ± 11.4 | 40.7 ± 8.2 | 0.12 |
| Tissue Doppler S wave (cm/s) | 13.7 ± 2.1 | 13.8 ± 2.1 | 0.86 |
| Tissue Doppler e wave (cm/s) | 17.2 ± 4.5 | 14.3 ± 3 | 0.01 |
| Tissue Doppler a wave (cm/s) | 12.6 ± 3.1 | 13.1 ± 3.1 | 0.50 |
| RVIVA ($m/s^2$) | 2.92 ± 0.69 | 3.4 ± 0.68 | < 0.01 |

$p < 0.05$ statistically significant. Continuous variables are reported as mean ± SD or median (IQR). Categorical variables are reported as *n* (%).
RVEF: right ventricular ejection fraction, TAPSE: tricuspid annular plane systolic excursion, RVFAC: right ventricular fractional area change, MPI: myocardial performance index, RVIVA: right ventricular isovolumic acceleration, PW: pulsed wave.

Furthermore, an independent correlation was detected between the pulmonary artery diameter and heroin use in univariate [1.49 (1.19–1.85), $p < 0.01$] and multivariate [1.43 (1.14–1.81), $p < 0.05$] regression analyses (Table 3).

## Discussion

Addiction to heroin-like drugs is currently an important health problem however knowledge on the cardiac effects of heroin addiction is limited. To our knowledge, the present study is the first in the literature on the subject.

The effect of heroin use on cardiac function has been investigated in several studies previously. It was demonstrated in the study by Pons Llado *et al.* on patients using IV heroin that heroin use had no effect on left ventricular systolic or diastolic function, but significantly increased the rate of mitral and tricuspid valve abnormalities.[5] In another study, it was demonstrated that synthetic cannabinoids negatively affected left ventricular function, whereas heroin did not.[6] However, these studies do not provide any information on the effect of heroin addiction on right ventricular function.

Although heroin use does not seem to have any effect on left ventricular function, according to the results of these studies, others have demonstrated atrial and myocardial irregularities by histopathological sampling.[7] Orlando *et al*. reported a subclinical reduction in the ejection fraction of the left ventricle in 20 heroin addicts.[8] In another case report, cardiogenic shock was reported in a young heroin addict, which was related to severe depression of left ventricular contractility. However, the authors attributed this to another cause, right ventricular failure.[9] All these conflicting results suggest the need for further studies.

**Table 3. Multiple logistic regression analysis to detect independent factors related to heroin-using group**

| *Variables* | *Univariate OR,95% CI* | p-*value* | *Multivariate OR,95% CI* | p-*value* |
|---|---|---|---|---|
| RVIVA ($m/s^2$) | 0.36 (0.18–0.72) | < 0.01 | 0.42 (0.19–0.88) | 0.02 |
| Pulsed Doppler MPI | 16.4 (1.12–239.27) | 0.04 | 9.45 (0.51–172.1) | 0.13 |
| Pulmonary artery diameter (mm) | 1.49 (1.19–1.85) | < 0.01 | 1.43 (1.14–1.81) | < 0.05 |

MPI: myocardial performance index, RVIVA: right ventricular isovolumic acceleration.

The cardiac effects of heroin are not limited to myotoxic effects. It was reported in the study by Pavlidis *et al.* that myocardial infarction was observed rarely, but the mechanism is unknown. Increased cardiac weight, which is observed as a result of increased thickness of the cardiac walls, could be a factor and therefore should be investigated.[10]

In another case of heroin-related cardiac crisis, the authors attributed it to heroin-related cardiotoxic effects and vasospasm.[11] Furthermore, in studies investigating the mechanism of heroin-related arrhythmias and subsequent sudden death, it was demonstrated that heroin use did not only lead to myocardial infiltration, but also to fibromuscular dysplasia in the sinus and atrioventricular nodes, in the transmission pathways and to fat infiltration. They concluded that this may be the cause of arrhythmia-related sudden death in heroin addicts.[12,13]

Another important heroin-related problem is pulmonary oedema, which was demonstrated as one of the most frequent causes of heroin-related death. There are many studies in the literature on the subject,[3,14,15] however, the mechanism could not be clearly defined. Although the direct pulmonary effects have been primarily considered, depression in cardiac contractility has been suggested as a possible mechanism.

In order to better understand the mechanism of pulmonary oedema, which is an important problem in heroin addicts, the cardiac effects of heroin should be defined. However, when heroin is used via the IV route, it is administered together with additional chemical substances named adulterants (acetaminophen, caffeine, diphenhydramine, methorphan, alprazolam, quetiapine, chloroquine, diltiazem, cocaine, procaine, lidocaine, quinine/quinidine, phenacetine and thiamine), and the potential cardiac effects of these substances complicate evaluation of the cardiac effects of heroin.[16] Therefore in order to investigate the cardiac effects of heroin only, we excluded patients using heroin via the IV route.

This study demonstrated that heroin use significantly increased right ventricle and pulmonary artery diameters, and negatively affected the MPI and RVIVA. Assessing right ventricular performance is not easy and is underestimated in many studies. Generally, evaluation of more than one parameter is recommended.[17] Being a pilot study on the subject, our study is important, since it shows impairment in multiple parameters. However, it is notable that values such as TDI-S and TAPSE were unaffected. Further studies with larger sample sizes, using new techniques such as three-dimensional and strain echocardiography are needed to better define the subject.

Our study had some limitations; these were the single-centre design and lack of examinations such as three-dimensional and strain echocardiography during cardiac function investigations. Also this was a retrospective, observational study therefore it does not provide conclusive results in this regard.

## Conclusion

Heroin addiction, which is an important public health problem, negatively affects right ventricular function and more attention

should be paid to the cardiac function of these patients. Since present knowledge on the effect of heroin use on cardiac function is limited, this study is important for its contribution to the literature. However, further studies with a larger sample size are needed for clearer results.

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