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PAPER

PATHOLOGY/BIOLOGY; TOXICOLOGY

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Histologic Findings of the Sinus Node and the Perinodal Area in Street Heroin Addicts, Victims of Sudden Unexpected Death

ABSTRACT: Sudden unexpected death is frequent in street heroin addicts. We conducted a histologic study of the sinus node (SN) to offer some evidence about the possible arrhythmogenic cause of death. Postmortem coronary angiography and microscopic examination of the SN and the perinodal area were performed in 50 heroin addicts (group 1) and in 50 nonaddicts (group 2), all men (16–40 years old). In heroin addicts, fatty and/or fibrous tissue replaced SN tissue in 21 cases (42%). Perinodal infiltration was found in 15 cases (30%). Fibromuscular dysplasia in branches of the sinus node artery (SNA) was found in eight cases (16%). Inflammation with focal and/or diffuse concentration of round cells was detected in the SN in 22 cases (44%). Old mural thrombi were also found in 13 cases (26%). The histologic changes in the SN and perinodal area offer an explanation about the possible mechanism of arrhythmia and sudden death in this population.

KEYWORDS: forensic science, heart, atria blood supply, sinus node, heroin, heroin addicts, sudden death

Heroin addiction is an important and increasing health problem especially in young people. Various types of cardiac arrhythmias have been described in this population (1–4). Moreover, street heroin addicts frequently die suddenly, and there is evidence that this is an arrhythmia-related event.

We conducted an anatomic and histologic study of the sinus node (SN) in sudden unexpected death (SUD) victims. The purpose of this study was to compare these findings between street heroin and nonheroin addicts in an attempt to find possible morphologic differences explaining the cause of SUD in the former.

Materials and Methods

We examined histologically the SN and the perinodal atrial myocardium of 50 male street heroin addicts, victims of SUD (group 1). We compared our findings with those obtained from 50 men who died from traffic accidents and who did not have a history of drug addiction (group 2). The mean age of subjects in group 1 was 30 years (range 18–40) and of those in group 2 was 28 years (range 16–40).

All the aforementioned decedents were submitted to judicial autopsy at the department of Forensic Medical Service of Athens. Postmortem examination was performed within the first 24 h after death. The confirmation of heroin addiction was initially based on police and medical reports, autopsy investigation into the area where the body was found, circumstances at the time of death, discovery of injection material, or needle puncture signs in the body. Urine from the bladder and blood from the right internal jugular vein were collected at the time of autopsy and examined in our laboratory. The identification of the products of metabolism of heroin in the urine and blood from toxicologic analysis established the diagnosis in all heroin addicts.

The fatalities were included in group 1 only if both morphine and 6-monoacetyl-morphine (6-MAM) were present in their blood and urine as measured by gas chromatography/mass spectrometry (GC-MS). It should be noted that in addicts >32 years old, additional substances were identified (more frequently benzodiazepines, methadone, and alcohol).

After the macroscopic examination of the hearts, we injected different colored radiopaque medium (BaSO4) to make the coronary arteries and their branches visible. This material was injected into each coronary artery simultaneously at a pressure of 100–150 mmHg, depending on the size of the heart. Gelatin was not included in the injected material to avoid solidification in the vessel lumen, which makes sectioning difficult. However, owing to the absence of gelatin, the injected material did not remain into the lumen of sinus node artery (SNA) in some cases, as confirmed by histologic examination. After the injection of the contrast material, X-ray films of the intact hearts were taken in anteroposterior, posteroanterior, and lateral projections to identify the origin, course, and ending of each coronary artery. In the cases where abnormalities of the vascular lumen were noted, histologic examination in these areas was subsequently performed.

The SN and its surrounding area were studied under standard microscopy. Tissue samples were obtained through a vertical incision starting from the outer side of the orifice of the superior vena

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cava (SVC) following the ridge of the right atrium to its auricle. We took five tissue strips of 2 cm length and 2–3 mm wide parallel to the first incision, two anteriorly and three posteriorly to the SVC and the right atrium, similar to the method described by Hudson (5). The five strips were fixed in 10% buffered formalin and embedded in paraffin. Five continuous sections were taken from each strip (a total of 25 sections from each heart). The sections were stained either with hematoxylin–eosin or with elastica Van Gieson or Masson's trichrome stain. Double staining was applied in some of samples. Two independent pathologists blinded to the samples origin performed the microscopic examination of them.

Results

The hearts were of normal size. The mean heart weight was also normal in both groups, 290 g in group 1 and 280 g in group 2, respectively. Pericardial effusion of small amount was found in only five cases (10%) of group 1. Multiple petechiae of the epicardium and/or endocardium were seen in 15 cases (30%) of group 1 and in only three (6%) cases of group 2.

In 55 of the total 100 cases, SN was perfused from the right coronary (RC) artery (Fig. 1). The artery encircled the sinoatrial ring clockwise in 18, counterclockwise in 31, and from both sides in six cases as viewed from above. In 34 cases, SN was perfused from the left circumflex (LCx) coronary artery, coursing clockwise in 12, counterclockwise in 18, and from both sides in four cases. In the remaining 11 cases, blood to the SN was supplied through branches either from both RC and LCx or from one of them (two branches) joining to form a circle around the SN area. The course of SNA was a useful marker to identify the location of the SN passing through the middle of it in the majority of our cases (78%). The SNA beyond the SN supplied part of the atrial myocardium and of the interatrial septum in accordance with our previous report (6). The SN was located in the lateral aspect of the superior cavo-atrial junction, in the sulcus terminalis, below the crest of the right atrium appendage in 78 and straddling the crest in 22 cases.

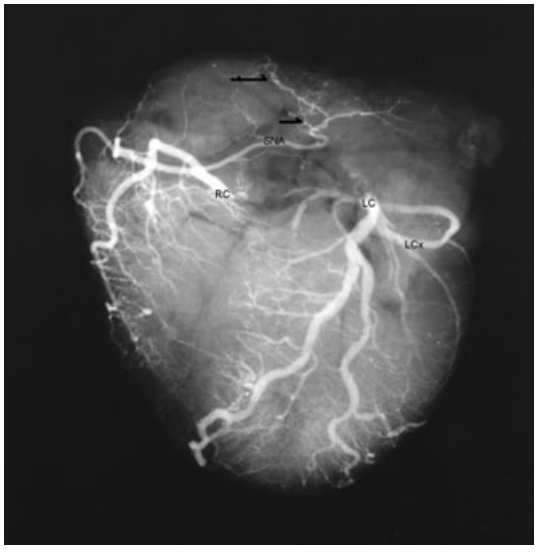

FIG. 1—*Postmortem angiography showing the origin, course, and ending of the sinus node artery (SNA) in one drug-addict case. Small arrow shows anastomoses in the interatrial septum, and large arrow shows the sinus node (SN) area. RC, right coronary artery; LC, left coronary artery; LCx, left circumflex artery.*

Histologically, as clearly shown in group 2 cases, the SN tissue was composed of two specific types of myocardial cells, the round or oval p cells and the slender transitional cells. Nodal cells were smaller than the atrial myocardial cells and were branching and interwoven so that some of them appeared cut transversely and others at various angles. Collagen and elastic fibers were observed among the SN muscle cells significantly more abundant than those found in atrial myocardium, creating thus a distinct border between them (Fig. 2). More detailed descriptions of the location, anatomy, and histology of the normal SN and its perfusing artery have been reported elsewhere (5–9).

The differences between the two groups regarding the histology of the SN and the perinodal tissue are presented in Table 1**.**

More specifically, in group 1 samples, the SN tissue was replaced by small to moderate amount of fatty and/or fibrous tissue (Fig. 3) in 16 cases (32%) and by marked amount in five cases (10%). In three of the last five cases (all of them >34 years old), only some thin rims of the SN fibers had remained as a sign of surviving nodal cells (Fig. 4). In the remaining 29 cases, (58%) the fatty and/or the fibrous tissue component was within normal limits. In the group 2 samples, only a small amount of fat and/or fibrous tissue infiltration of the SN was found in seven cases (14%; all of them >33 years old).

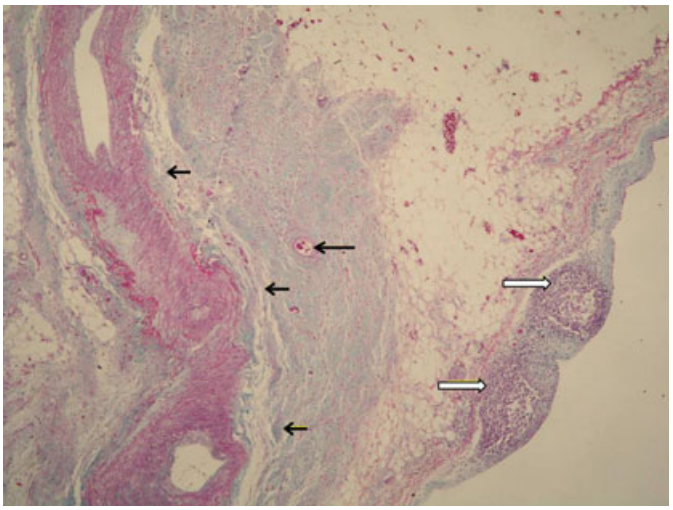

FIG. 2—*Photomicrograph showing normal sinus node (SN) tissue with a small branch of the sinus node artery (SNA) in the middle of it (large arrow). In the right side of the picture, two inflammatory foci (90% lymphocytes, 10% plasmocytes) at the subepicardium besides the SN (open arrows) are shown. On the left, the junction of the SN tissue with the atrial myocardium (small arrows) is shown. Masson trichrome stain, orig × 4.*

TABLE 1—*Histologic features of the sinus node tissue and the surrounding area in the two groups.*

Histologic Features	Group 1 (%)	Group 2 (%)
Replacement of SN tissue by fat/fibrous tissue	42	14
Replacement of nerves and ganglia by fat/fibrous tissue	30	0
Fibromuscular dysplasia	16	0
Inflammatory infiltration of the SN and its surrounding area	44	6
Mural thrombi RA/RAA	26	0
Atherosclerotic lesions of intima	22	24

SN, sinus node; RA, right atrium; RAA, right atrium appendage.

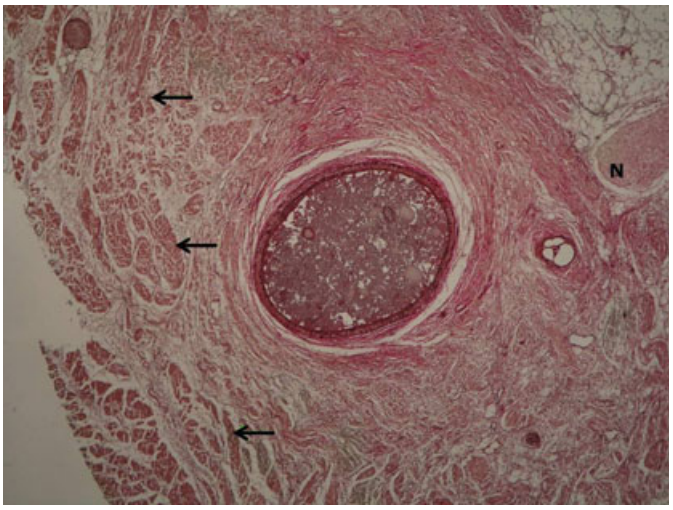

FIG. 3—*Photomicrograph showing the sinus node (SN) tissue mildly to moderately replaced by fatty and fibrous tissue. The sinus node artery with injected material in its lumen is located in the center of the SN tissue. Part of the longitudinal muscle of the artery has been replaced by the adventitia. On the right, subendocardial fat and a nerve (N) are seen, and on the left, the junction with atrial myocardium is indicated with small arrows. Elastica Van Gieson stain, orig × 4.*

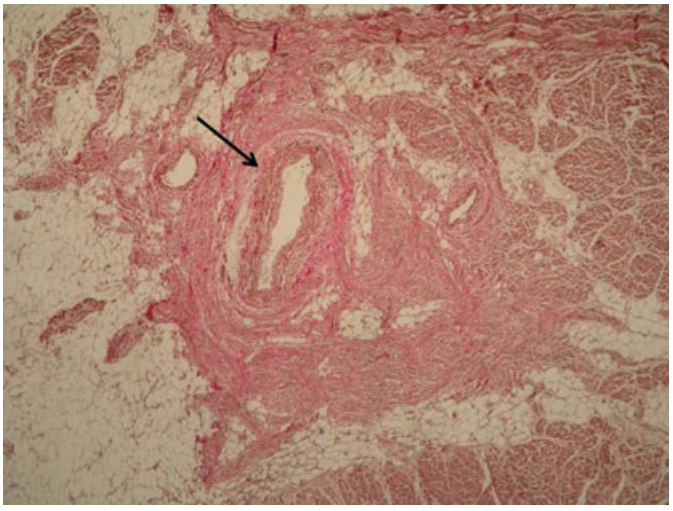

FIG. 4—*Photomicrograph showing destruction of the sinus node (SN) tissue. Marked amount of fibrous and fatty tissue have replaced the SN fibers. Small amount of surviving SN fibers remain around the sinus node artery (SNA) mainly on the right of it. The SNA is pointed with the arrow. Elastica Van Gieson stain, orig × 4.*

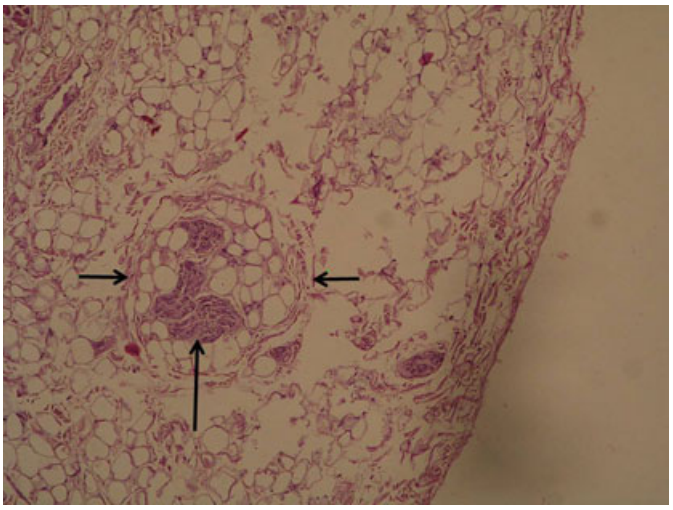

FIG. 5—*Nerve with some of its surviving fibrils (large arrow). The rest of the fibrils have been replaced by fatty and fibrous tissue. Small arrows point the perineurium. Hematoxylin–eosin stain, orig × 10.*

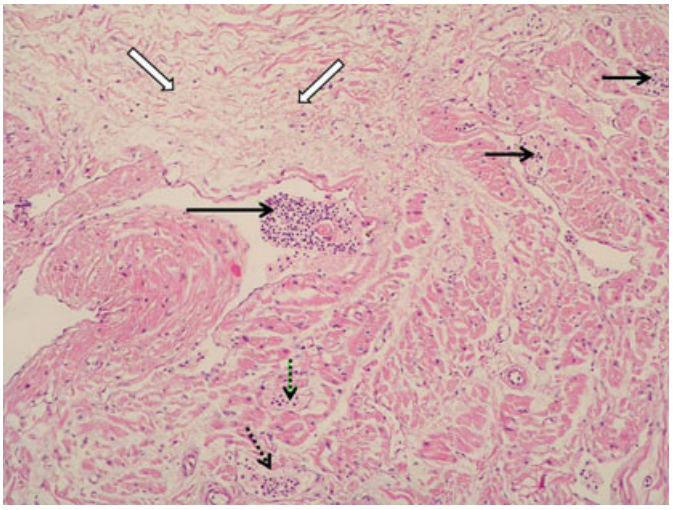

FIG. 6—*Histologic specimens of atrial myocardium showing many inflammatory foci, indicated with small arrows. Mural thrombus is attached to the endocardium (large arrow). Open arrows point to the area where fibrous tissue has replaced the atrial myocardium. Dotted arrows point to the atrial myocardium. Hematoxylin–eosin stain, orig × 10.*

In 22 cases (44%) from group 1 (Figs 2 and 6), focal and diffuse concentrations of inflammatory cells (round cells) were also found. These cells were located most frequently in all three cardiac layers in 18 cases (36%). The second most frequent location was in the endocardium, with a histologic appearance of either an active inflammation or a healed one or both in 15 cases (30%). In 11 of these 15 cases, inflammatory changes co-existed in all three layers, while in the rest four cases inflammation was limited strictly to the endocardium. Associated myolysis, interstitial edema, and fibrosis were also found. Only three cases with focal inflammatory infiltration in all cardiac layers were found in group 2.

Moreover, the following histologic changes were found only in group 1 samples: inflammatory or degenerative changes in the ganglia and nerves surrounding the SN (Fig. 5) in 15 cases (30%), old mural thrombi of various ages partly organized with the endocardium of the right atrium and/or its appendage (Fig. 6) in 13 cases (26%), and fibromuscular dysplasia in some of the small branches of the SN artery in eight cases (16%).

In 11 cases from group 1 and in 12 cases from group 2 (all of them >29 years old), mild atherosclerotic changes in the intima of all coronary arteries and their branches were noted.

Discussion

We presented our histologic findings from the study of the SN and the perinodal atrial myocardium in 50 male heroin addicts, victims of SUD. To our knowledge, such findings mainly characterized by the loss of normal SN cells and nerve fibers, inflammatory infiltration, and formation of mural thrombi have not been previously reported.

Moreover, we compared the histology of the drug-addict hearts with those of 50 male nonaddict hearts of similar age to find morphologic differences explaining the various arrhythmias in the former as has been described by others (1–4).

Loss of myocardial SN cells, replaced by various amounts of fatty and/or fibrous tissue, was found in 42% of the heroin addicts group but in only 14% of the nonaddicts group. In our opinion, this type of degeneration of normal SN tissue may be related to the development of SN dysfunction and may indicate arrhythmia as the mechanism of sudden death in this population. Other studies have reported that there are no specific histologic features in the myocardium of drug addicts to distinguish them from controls. However, SN pathology was not examined in any of these studies (10–12).

Inflammatory infiltration of the SN and surrounding area was found in 44% of heroin addicts and in only 6% of controls. Inflammation frequently affected all cardiac tissue layers (36% of the inflammatory cases). Such changes mainly affecting the myocardium at a range of 3.4–17% have been previously reported by others (11,12). In addition, inflammatory changes in the endocardium were found in 30% of our cases. Others have reported endocarditis in up to 47% of their cases (13,14). However, not everybody agrees that drug addicts develop endocardial inflammation (10,11). In any case, infiltration of the SN by inflammatory cells has not been previously reported. These inflammatory findings can probably be attributed to admixtures of the heroin or to the nonsterile injection techniques of intravenous drug users.

Myocarditis alone is responsible for 25% of sudden death in young people (15). Probably, the inflammatory infiltration acts on the SN and its surrounding area through the toxins and the development of myolysis, interstitial edema, and fibrosis, which may facilitate the initiation and the perpetuation of different types of arrhythmias.

Inflammatory infiltration and degeneration changes were found in the ganglia and the nerves in 15 (30%) of group 1 cases. The degeneration of the ganglia and nerves probably had been developed from the effect of heroin or from toxins because of the inflammatory process possibly leading to malfunction of them. Mural thrombi in the right atrium and its appendage were found in 26% of group 1 cases, probably due to endocarditis. These thrombi may lead to microembolization. Fibromuscular dysplasia of the vessel wall in some of the small vessels of the SNA was observed in eight (16%) heroin addict cases.

Heroin does not seem to directly affect the coronary arteries and their branches as we did not find differences in the atherosclerotic changes between the two groups. There are studies in the literature supporting mainly the effect of cocaine and less that of heroin in the coronary vessels (16,17). Fibromuscular dysplasia of the vessel wall in some of the small vessels of the SNA was observed in eight (16%) heroin addict cases.

Based on our results, we postulate that street heroin along with its admixtures and with the use of nonsterile techniques affects the SN and the surrounding nerves, ganglia, and atrial myocardium replacing their tissue with amounts of fatty and/or fibrous tissue. These changes may result in dysfunction of the aforementioned structures and probably in the origin of different types of arrhythmia.

A major limitation of our study is that our findings may reflect the effect of street heroin, of its admixtures, or of both on the SN histology. However, these are real-life findings, and only an experimental study could offer further evidence about the pure effect of street heroin on the myocardial tissue.

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