Cardioneuropathy and Extracardiac Neural Disease

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The pathology of cardiac innervation, both intrinsic and external to the heart (aortopulmonary glomera included), is scarcely known, yet it can be critical to life-threatening disorders in cardiac performance, or to reflexes discharging outside the heart, or both. Evidence has been supplied in cardiac neuroanatomy relevant to cardioneuropathy. The arrhythmogenic potential of imbalanced autonomic input in the heart has been corroborated by histopathologic findings in intrinsic plexuses. In turn, significant neurogenic substrates for cardiomyopathy have not been confirmed. Changes in the extrinsic sympathetic chain (left stellate ganglion) and in the prevailing vagal cardiac plexus were found in subjects with arrhythmias (with long QT interval and ventricular tachycardia/fibrillation, respectively).

In myocardial infarction with sudden cardiac death, a complicating mediastinitis often presented and was seen to produce focal inflammation of mediastinal nerve plexus and paraganglia. This can worsen the imbalance in autonomic control of the performance of the heart and interfere with barochemoreflex regulation of the systemic or coronary circulation, or both. Such ill-understood sequelae of infarction as the shoulder-hand, chest pain and Dressler syndromes might also correlate with the newly described neuromediastinitis.

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The enlightening prophecy by Leonardo da Vinci (1) about the overall importance of cardiac morphology and the role of nerves in the heart's action met only a half-hearted acceptance. Indeed, basic neuropathology of the heart has been sadly neglected and calls for a much better documentation than hitherto available.

Relying on the first sound nosographic assessment of cardioneuropathy (2), this report will attempt to contribute further details of the intrinsic and extrinsic innervation of the heart as a premise to gain a better insight into ill-understood anatomoclinical correlates.

Methods and Criteria

For the purpose of this study, 120 exemplary specimens (both autopic and biotic) have been taken from my personal collection. Light microscopic examinations were carried out on the intrinsic atrial and ventricular nerve plexuses. Because the extrinsic nerve supply to the heart is too rich, complex and elongated (3,4) to allow for exhaustive control, investigation in selected cases was limited to the left stellate ganglion, the right thoracic vagus with its branchings into the cardiac plexus (3) (intended in a broad sense) and the annexed aortopulmonary paraganglia (at the fourth to sixth branchiomeretic level [5]). Small ganglia adjacent to glomoid structures above the root of the left coronary artery were also examined. Technical details of the treatment of the specimens have been described previously (6).

For tentative clinicopathologic reasoning, the conventional well grounded idea of imbalance and asymmetry in autonomic control of the heart (2) was retained, also inferring some disorder in cardiocirculatory reflexes, whenever mediastinal barochemoreceptors were involved.

Cardiac Neuroanatomy and Pathology

Intracardiac innervation consists of a ganglionated and a coarse plexus, further resolving into a fine network of small trunks and preterminal fibers throughout the heart (7). Not only postganglionic fibers travel the coarse plexus (7), as shown by the presence of scattered neurons in ventricular nerves. Scanty evidence of afferent terminations is available in animals (8). Similar terminations have been observed in human atria, consisting of bare multidirectional axons, criss-crossing one another. Realizing that morphology of intracardiac receptors is as yet unknown (4), one could view these nerve endings and their geometric arrangement as being consistent with the features of a mechanoreceptor that is excitable by directional stretch (9). Mediastinal glomoid structures can be regarded mostly, if not exclusively (5), as barochemoreceptors.
Axonal beads that store autonomic mediators (granular and agranular vesicles for catecholamines and acetylcholine, respectively) (10) can be detected in the heart. However, the light microscope does not allow for a discrimination between vagal and sympathetic fibers.

The changes of cardiac nerves and ganglia share the usual features of peripheral autonomic neuropathy (2,6,11).

**Intrinsic Neuropathology in Atrial Arrhythmias**

Cardioneuropathic changes were observed in a number of cases presenting with atrial arrhythmia such as sustained sinus tachycardia and sinus arrhythmia, atrial fibrillation, sinoatrial block and sick sinus syndrome (12). In the latter arrhythmia, intrinsic nerve changes alone were occasionally seen to cause pacemaker dysfunction (6).

Neural changes damaged the rich sinoatrial plexus or the intranodal nerves, or both; also, those nerves coiled around the artery of the sinoatrial node, with a possible bearing on a pulsatory servomechanism (13) and inherent disturbances of the pacemaker function. In the case of atioventricular (AV) junctional escape rhythm, among similar neural abnormalities, a pronounced swelling and vacuolation (6) of the axonal “beads” was detected in atrial nerve fibers (by abnormal storage of chemical neurotransmitters).

**Ventricular Tachyarrhythmias and Neuropathology of Infarction**

An example of deranged autonomic control of the heart, correlating with sudden death from ventricular tachycardia/fibrillation, is represented by myocardial infarction. Early in the ischemic attack, complex autonomic disturbances occur and interact, which submit the heart to a bombardment of imbalanced stimuli and to a reflexogenic storm involving the whole intrinsic and extrinsic innervation up to the psychic sphere.

Little is known about the morphologic substrates of such a neural debacle (14). It has been suggested that both sympathetic and vagal mechanoreceptors, unevenly distributed in the infarcted ventricle would be excited primarily by stretch, with discharge (15) into intrinsic and extrinsic nerve pathways. Lately, histochemical evidence of catecholamine depletion of neural vesicles was obtained in acute experimental infarction within (16) and apical to (17) the damaged zone. This evidence was interpreted as an exaggerated release of norepinephrine into the ischemic myocardium (16), and was regarded as a functional sympathetic denervation (17). Anatomically, intracardiac nerves withstand early ischemic injury, only exhibiting minor changes (epiperineurial edema) while the nearby muscle succumbs to necrosis. Actual denervation by multiple axonal disruptions presents 24 to 48 hours later at the successive stage of leukocytic infiltration inside and around the necrotic area.

Nerves are less dependent on aerobic metabolism than is the myocardium; hence, secondary inflammatory involvement, rather than primary ischemic injury, seems to be responsible for severe disruptive damage of the infarcted cardiac plexuses (12). To confirm the discrepancy between neural and myocardial involvement in infarction, it can be seen that some nerves even survive the stage of granulation and scarring. In turn, neuronal loss, with replacement by capsular cells (Terplan nodules) (Fig. 1) may present in sinoatrial ganglia of the infarcted heart (14) far from the area of necrosis, which is yet hard to explain.

**Figure 1.** Left coronary artery ganglion (close to paraganglion), from a girl who died suddenly with rheumatic cardiovalvular disease. There is advanced degeneration of neurons, with replacement by Terplan nodules. (Original magnification ×500; reduced by 29%.)

**Figure 2.** Inflammatory changes of the left stellate ganglion surgically ablated from a young woman with long QT syndrome and high risk tachyarrhythmias. The syndrome subsided after operation. (Original magnification ×500; reduced by 29%.)
Neuropathology of Cardiomyopathy

Intrinsic neuronal depletion was believed to underlie dilated cardiomyopathy (18), Chagas' disease (19) and diabetic cardiopathy (20) and to account for parasympathetic denervation and imbalanced sympathetic overactivity. Perhaps a neural pathogenesis has been overemphasized; in my experience, infantile dilated cardiomyopathy can occur in the presence of mild sinoatrial ganglionitis without neuronal depletion, and well preserved ventricular nerves (containing nerve cells) were seen in the hearts of patients with Chagas' disease just as pointed out in a recent study on Brazilian patients (19). Diabetic denervation of the heart is rare (20); neural changes in atrial nerves were observed in only 1 of my 10 cases.

Extrinsic Cardiac Neuropathology

Exaggerated sympathetic input in the heart through the left stellate ganglion is regarded as critical to QT interval prolongation and inherent arrhythmogenic risks (2,21). Preliminary histologic control (under study with P. J. Schwartz) of left stellate ganglia from five surgically treated patients with the long QT syndrome has disclosed occasional inflammatory (22) (Fig. 2) or degenerative changes. The same applies to the left stellate ganglia surgically ablated from patients with myocardial infarction, to prevent recurrent episodes of ventricular fibrillation that were occasionally heralded by symptomatic QT interval prolongation (23). These pathologic findings are reminiscent of those described in sympathetic ganglia excised from patients with obstruc-
tive limb arteriopathy (24), and their etiology is highly uncertain.

Little is known about disordered parasympathetic action on the heart from disease of the cardiac plexus (mainly vagal), with involvement of aortopulmonary juxta or intra-vagal paraganglia. In a case of mediastinal invasion from bronchogenic carcinoma with disruption and compression of the cardiac plexus, the patient presented with and died from intractable paroxysms of ventricular tachycardia/fibrillation. In a young girl with chronic rheumatic carditis, in the Dressler syndrome. Medial neuritis and paraganglionitis from infarction

In eight patients with acute myocardial infarction and in one with lung infarction dying suddenly, an unexpectedly high incidence of neuromediastinitis was observed (ongoing research with L. Matturri and P. Cazzola). Apparently, the more or less conspicuous inflammatory reaction to myocardial ischemic necrosis, whether or not involving the pericardium, may extend to the mediastinal interstitium; the same applies to pulmonary infarction. This seems to occur either by contiguity or through the lymphatics, or by both mechanisms.

Though clinically overlooked, this mediastinal inflammation with polymorphic (Fig. 3) or round cell (Fig. 4 and 5) infiltrates, may entail serious neuropathologic hazards insofar as it attains the cardiac plexus (Fig. 3 and 4), the annexed paraganglia (Fig. 5) and the ill known glomoid structures (25-27) (intravagal [Fig. 6] and para-arteriolar) that are profusely distributed throughout the area. Epineuritis (Fig. 3), endoneuritis (Fig. 4) and abnormalities of nerve cells or Zell ballen (Fig. 5), or both, are reasonably expected to interfere with the autonomic control of the cardiovascular system with manifold pathophysiologic implications.

Conclusions

More has been learned in cardioneuropathology, both intrinsic and external to the heart, with significant involvement of mediastinal glomera as well. Thereby, a broader insight can be gained into far-reaching anatomoclinical correlates from high risk deterioration of cardiac performance (namely, arrhythmias) to critical impairment of baro- and chemoreflex control of the systemic or coronary circulation, or both (26-28). Moreover, the pathologic notion of subclinical neuromediastinitic sequelae of myocardial infarction may help to interpret such intriguing manifestations as pain in the shoulder and hand or chest wall syndrome, and pleuritis, in the Dressler syndrome.

On the whole, beyond the extent uncertainties, the importance of the multifaceted aspects of cardioneuropathy clearly emerges in the proper assessment of major problems in modern cardiology (29).

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