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Presence of Ganglia and Brown Fat in Human Atrial Pericardium: Histology Characterization

Presencia de Ganglios y Grasa Parda en el Pericardio Atrial Humano: Caracterización Histológica

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RODRÍGUEZ, H.; ARRIAZA, C.; RODRÍGUEZ, N.; ARAYA, J. C. & ESPINOZA-NAVARRO, O. Presence of ganglia and brown fat in human atrial pericardium: Histology characterization. *Int. J. Morphol., 43(6)*:2123-2128, 2025.

SUMMARY: Cardiac contraction is performed by contractile stimuli of the specific myocardium and by sympathetic and parasympathetic regulation, whose nerve ganglia are located at the level of the mediastinum. This study analyzes other nerve pathways organized in ganglion units in the human atrial pericardium and surrounding brown fat. Human samples from the right atrium, obtained and authorized by the Faculty of Medicine of the Universidad de Chile, were fixed in 10 % formalin for 48 hours (5 µm sections). For histological analysis of the samples, routine hematoxylin and eosin and special techniques of toluidine blue, orcein, and van Gieson staining were used for the observation of Nissl bodies, elastic fibers, cytoplasm, collagen, and brown fat, respectively. Immunohistochemistry techniques were used to recognize the presence of neurofilaments and S100 protein (DAB). The histological and immunocytochemical analysis revealed the presence of a ganglion composed of globose neurons that reacted positively to the recognition of neurofilaments, distinctive elements of the cytoskeleton of neurons. The cells surrounding the neurons were shown to be positive for S100 protein. Additionally, subepicardial brown fat was observed. The study concludes by demonstrating and describing the presence of well-formed ganglia in the subepicardial connective tissue, with abundant brown fat. The presence of ganglia and brown fat could explain some symptoms and pathologies of unknown origin, such as angina and sudden death.

KEY WORDS: Anatomy; Pericardium; Ganglion; Human; Cardiac fat.

INTRODUCTION

The pericardium corresponds to a mesodermal mesothelial derivation organized into a parietal mesothelium and a visceral mesothelium or epicardium, forming the pericardial cavity. However, the epicardium corresponds to a simple, flat, mesothelial epithelium adherent to its lamina propria and chorion together with the adjacent myocardium, although also separated from it by a variable connective tissue with abundant multilocular or brownish fatty tissue. Blaszkiewicz *et al*. (2019) determined that brown and white adipose tissues are essential for maintaining energy balance and metabolic health; their composition is currently receiving particular interest in studying the homeostasis of heart structure and function (Matloch *et al*., 2016, 2018). At the ventricular level, the pericardium consists predominantly of adipocytes, immunocompetent cells, ganglia (reduced to only nerve fibers), and branches of nervous tissue.

Similarly, it is described that eventually, the pericardial fat would form part of the cardiac skeleton to support the intrinsic innervation of the heart, describing the presence of epicardial ganglionic plexuses: 5 in the atrium and 6 in the ventricles, although all related only to the description of nerve fibers directed towards the heart. These neurons could be responsible for the origin of angina pain and "ángor pectoris" (Balla *et al*., 2018; Fedele & Brand, 2020; Giannino *et al*., 2024).

The innervation of the heart is described based on sympathetic ganglionic systems and distribution in the mediastinum. This approach suggested the concept of ganglionic plexuses (GP), which consists of grouping ganglia at different sites (Pauza *et al*., 2002; Kuder & Nowak, 2015; Aksu *et al*., 2021). Therefore, the presence of neuronal bodies

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organized in ganglion units in the human atrial pericardium has not been morphologically demonstrated. Thus, this study aims to histologically analyze the existence of other nerve pathways organized in ganglion units in the human atrial pericardium and the surrounding brown fat.

MATERIAL AND METHOD

Samples. Samples from the right atrium of a 67-year-old male cadaver from voluntary body donors, obtained according to established protocols and in compliance with current regulations (Faculty of Medicine, Universidad de Chile, 2022), were fixed by immersion in a 10 % Formalin fixative solution (from a 37 % stock solution) prepared in phosphate buffered saline pH 7.2.

Histological techniques. Following 48 hours of fixation, the specimens were subjected to routine histology procedures, with Hematoxylin and Eosin staining in 5 μm sections. Other sections were treated for 0.1 % toluidine blue staining to reveal the presence of Nissl granules in the neuronal soma, orcein staining to recognize elastic fibers in their distribution and thickness (intense pink to brown), and Van Gieson staining to differentiate red collagens and yellow-brown cytoplasm of the different cell types present.

Immunocytochemistry techniques. Additionally, the samples were processed for immunocytochemistry (HCC) for the recognition of intermediate filaments in the soma of neurons and S100 protein to recognize glia analogs in the peripheral nervous system, with technical processes of labeling with diaminobenzidine (DAB) (primary antibody for neurofilament ab-1 2F11, ms-359-S1 neomarkers and primary antibody for S100 Protein [4C4. 9] (M), from BIO Care Medical), both techniques using Harris hematoxylin contrast.

Tissue analysis. Observations were performed with an OLYMPUS CX31 optical microscope using 4x, 10x, 40x and 100x objectives. The microscope has a built-in digital camera, the AmScope model MU1803, connected via USB 3.0 to the computer (PC) with the AmScope 3.7 digital camera app. During the observations, the areas of the epicardium (mesothelium and underlying connective and contractile myocardium) were reviewed. The results were displayed by obtaining digital photographs of the relevant findings.

RESULTS

The histological analysis of the human atrium at the subpericardium level shows the presence of well-constituted ganglion-like nerve organizations, nerve fibers, and somas of neurons positive for the presence of neurofilaments and pericytes positive for S100 proteins, both by immunohistochemistry techniques with specific antibodies (Fis. 1-6).

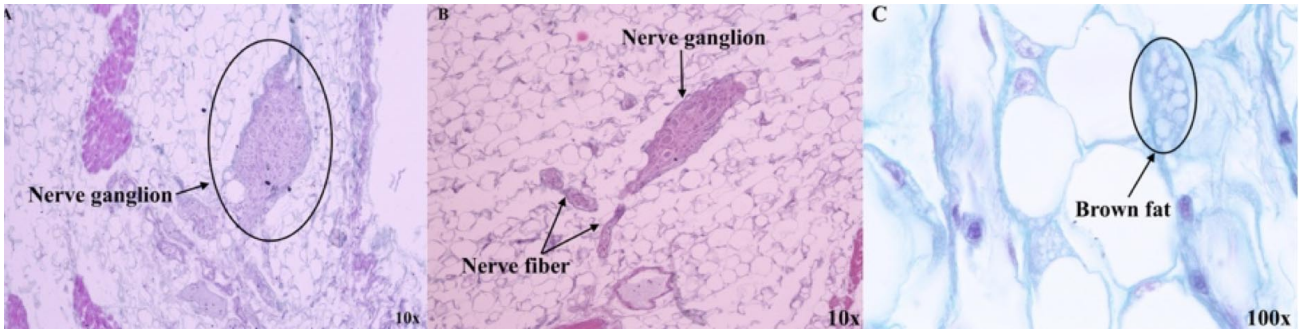

Fig. 1. A. The microphotographs of the human atrial subepicardium show the general morphology of the subepicardial connective tissue (circled); B. Highlighting the nerve ganglion with the somas of globose neurons and nerve fibers (arrows) 1C. Brown or multilocular fat (circled). Hematoxylin/eosin staining.

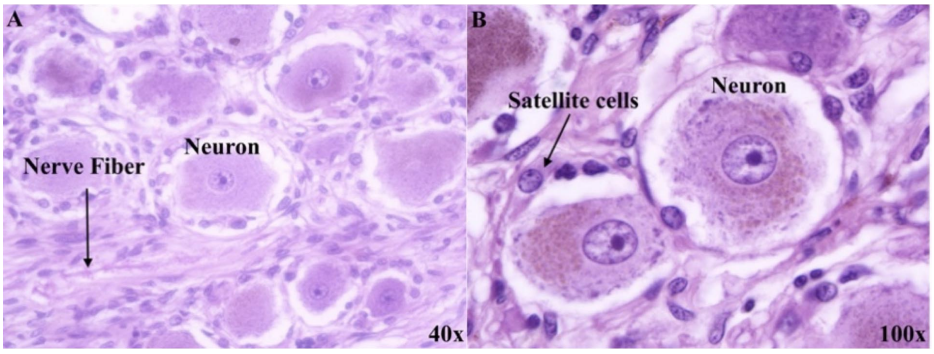

Fig. 2. A. The microphotograph shows the specific morphology of the pseudounipolar and globose neurons in the chorion of the epicardium of the human cardiac atrium. Arrows indicate nerve fibers. Fig. B. Satellite cells surrounding globose neurons (arrows). Granular lipofuscin brown staining is also observed in the cytoplasm. Hematoxylin/eosin staining.

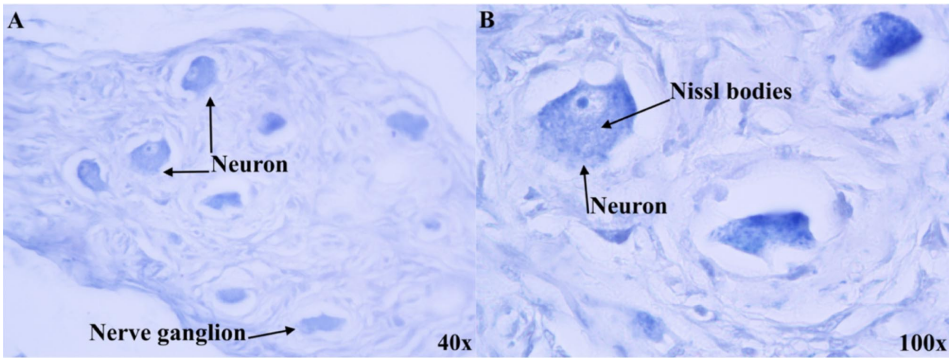

Fig. 3. A. Globose neurons and their nerve ganglia are observed in a microphotograph of the human atrium. B. Shows a neuron with abundant Nissl granulations (arrows).

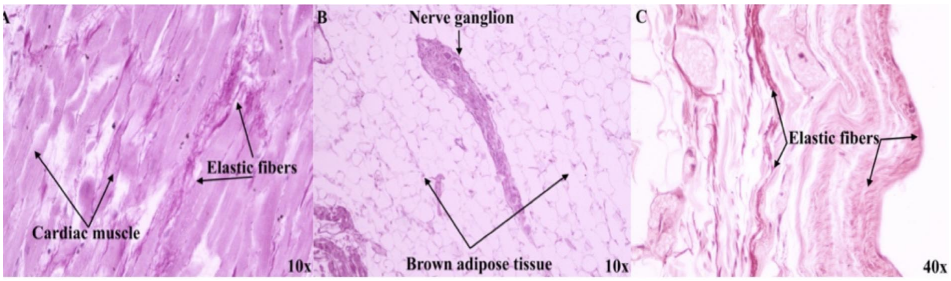

Fig. 4. A. The microphotograph of the human atrium (orcein staining) shows myocardial muscle cells with abundant elastic fibers (arrows). B. In the subepicardial nerve ganglion, a large amount of brown multilocular fatty tissue is observed (arrows). C. In the subepicardial connective tissue, abundant elastic fibers are shown in different directions, layers, and thicknesses (arrows). Staining Van Gieson's technique

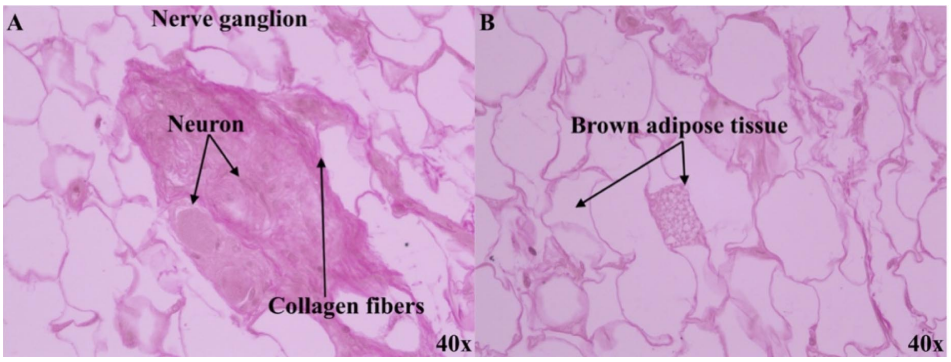

Fig. 5. A. The microphotograph shows that in the subpericardial region of the atrium, arrows indicate the presence of collagenous fibers and neuron cytoplasm with scarce connective tissue around the nerve ganglion (arrows). B. The arrows highlight abundant multilocular or brown fat employing the staining Van Gieson's technique.

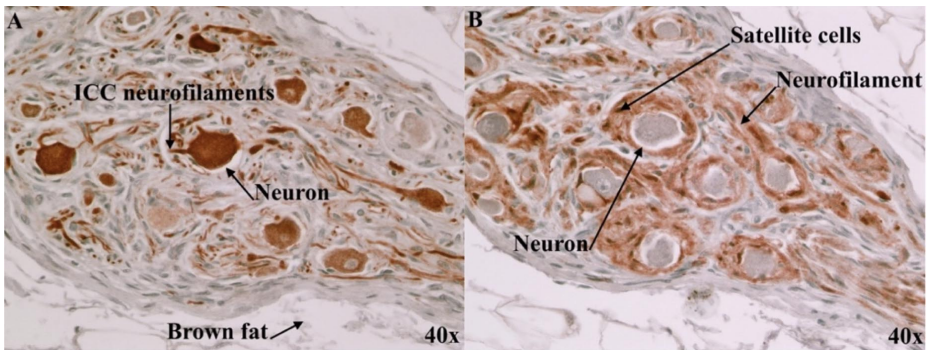

Fig. 6. A. Through immunocytochemistry (ICC: S100 protein), the microphotograph shows the somas of pseudounipolar or globose neurons, positive for the presence of intermediate filaments of the cytoskeleton (neurofilaments) of intense brown color (arrows) and their projections (axon and dendrites). There is also brown fat (arrow). B. Arrows indicate globose neurons and their projections (axons and dendrites), surrounded by satellite cells.

DISCUSSION

Various reflex mechanisms necessary to enable and regulate central blood volume (CBV) and mean arterial pressure (MAP) have been described, including the presence of baroreceptors for this purpose. These neuronal sensors are related to the brainstem and higher brain regions. They are capable of generating an optimal autonomic response, which includes adjustments in the parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) (Kimmerly, 2017; Fedele & Brand, 2020).

The cardiac sympathetic nerves innervate the walls of the heart, arising from the stellate ganglia (or cervicothoracic ganglion), which is a sympathetic ganglion formed by the fusion of the inferior cervical ganglion and the first thoracic ganglion, which exists in more than 80 % of individuals. Sometimes, the second and third thoracic ganglions are included. They are the ones that maintain the electrical activity of the heart (Wang *et al*.,2018).

Typically, the histology of the tissues and compartments of the heart only describes the cardiac nervous system associated with regulation by the sympathetic and parasympathetic nervous systems (Li, 2022), adding the projection of mediastinal ganglia (Campos *et al*., 2018). However, it is also necessary to highlight the presence and distribution of the specific myocardium.

The specific myocardium corresponds to smaller myocardiocytes than the contractile myocardiocytes. It is distributed in the subendocardial regions in the right atrial (P wave of the electrocardiogram), atrioventricular (PR segment of the electrocardiogram), and the one extending through the entire subendocardium in both ventricles (QRS complex of the electrocardiogram) nodes. These specific or conduction myocardiocytes have low amounts of contractile proteins (myosin and actin), few intercalary discs, and adopt a spherical or rounded shape (Keepers *et al*., 2020).

The ganglion neurons analyzed in this study (Figs. 1 to 6) show a large number of proteins gathered in the form of basophilic cytoplasmic granules known as Nissl bodies, which, according to the literature, are associated with the endoplasmic reticulum, being one of the characteristic features of nerve cells (Sree *et al*., 2021).

The pericardium has a simple flat mesothelial lining epithelium with a rectangular cell shape, a prominent nucleus, an oval shape, and its significant axis parallel to the surface. This epithelium is generally arranged straight on the organ's surface (Hemdan *et al*., 2024).

The subepithelial connective tissue of the pericardium is composed of various fibrous elements (collagen I bundles) of varying density but with an abundance of large unilocular adipose cells (white fat). Smaller numbers of multilocular fat cells or brown fat, as seen in Figures 1C and 4B. In the fibrillar extracellular matrix stained with orcein elastic fibers are observed, the elastic fibers of the pericardium/epicardium present a quite particular organization in the subepithelial region, arranged as a lattice perpendicular to the epithelial lamina (4C). Immediately after that, in-depth, the elastic tissue becomes thicker and intertwined bundles forming a base parallel to the anterior and mesothelial epithelial lamina. In the deeper connective tissue of the pericardium, adipose tissue strongly predominates, characterized by a thin outer sheath of thin, circular bundles of elastic fibers. Similarly, these patterns are repeated in the lymphatic and blood vessels. The latter has a substantial and prominent outer elastic membrane (Kamrani *et al*., 2025).

The presence of fat plays a multitude of essential roles in cardiovascular survival and function. Brown fat is typical of some regions of the newborn's body, and its presence signifies a state of biochemical protection against the presentation and development of metabolic diseases of the heart. With advancing age and obesity, it is reduced, and an increase in white fat appears (Aldiss *et al*., 2017). The associated excess of visceral fat in the heart and coronary arteries is a significant risk factor for the development of cardiovascular disease. Adipose tissue dysfunction involves the secretion of multiple factors that modulate vascular function and atherogenesis by damaging the elastic fibers of the connective tissue (Jääskeläinen *et al*., 2023). Brown fat in humans is typically distributed in the regions of the neck, clavicle, and around the spine. It is characterized by the use of glucose and lipids for heat generation, is intimately related to metabolism in the tissues that structure the heart, and functions as an actual organ of thermogenesis. The progressive reduction of fat in humans is closely related to obesity. These changes in fat types from multilocular to unilocular represent a consequential risk factor for cardiovascular disease (Cypess *et al*., 2009; Chen *et al*., 2021).

Embryologically, brown fat originates from mesenchymal cells of the splanchnic mesoderm, abundantly distributed in the submesothelial connective tissue of the epicardium, including the endocardium. The epicardium, with its mesothelial composition, simple flat epithelium, and underlying connective tissue with abundant brown fat, is directly continuous with the middle layer of the heart formed by myocardiocytes without a relevant limiting fibrous

connective tissue. The precise role of brown fat in the heart is scarcely understood, although its gene expression profiles are associated with cardiovascular risk. A relevant role in physical activity is played by the types of fat present, mainly related to thermogenic function and glucose consumption, characteristic of mainly brown fat (van Marken Lichtenbelt *et al*., 2009; Aldiss *et al*., 2018; Yoshida *et al*., 2022). The presence of brown fat improves the heart's metabolic state and reduces cardiovascular risks (Aldiss *et al*., 2017). The functions of pericardial fat are potentially related to myocardial energy, thermoregulation, protection of autonomic ganglia, local nervous tissue, and coronary arteries (Alcalá *et al*., 2019).

In the epicardium, the association and relationship of adipose tissue with atrial arrhythmogenic activity stands out, even more so when, in modern medicine, there are devices that allow the presence and tissue relationship of the atrium to be evaluated by noninvasive techniques (Wong *et al*., 2017). Currently, adipose tissue is ascribed a relevant endocrine function, the disruption of which would be involved in various endocrine, inflammatory, and cardiovascular pathologies, which together may have profound effects on the cardiovascular system and is a target tissue for potential therapeutic actions (Patel *et al*., 2017).

Epicardial adipose tissue (EAT) is recognized as a distinctly unique and multifaceted device. Due to tissue continuity, its proximity to the myocardium highlights endocrine, paracrine, and vasocrine functions directly to the heart. Pericardial fat accumulation and obesity are recognized as mobile factors of atrial fibrillation and of easy, noninvasive evaluation. Thus, there has been speculation that arrhythmogenic mechanisms may include adipocyte infiltration, pro-fibrotic and paracrine proinflammatory effects, oxidative stress, and other pathways so that variation and relationship in body fat distribution is another potential in association with local nerve tissue regionalization (Krishnan *et al*., 2022; Giannino *et al*., 2024).

Although the heart functions autonomously, the specific or conduction myocardium manages and regulates contractility. The cells obtain the energy for this function from glycogen stores. Contractile regulation is carried out through the sympathetic and parasympathetic systems, whose ganglionic relays are located in the regional mediastinum (Fedele & Brand, 2020; Raiko *et al*., 2020; Pinckard & Stanford, 2022; Li *et al*., 2023)

CONCLUSIONS

The histological and immunohistochemical techniques used indicate that it is possible to recognize in the subpericardial region of the human atrium the presence of nerve organizations based on ganglia with pseudo-unipolar or globose neurons and the presence of abundant brown or multilocular fat. The human atrium, at the level of the subpericardium and connective tissue, has its ganglia of classical organization. Particularly, the presence of brown fat mainly constitutes a vast energetic reservoir. The presence of ganglia and brown fat allows speculating on the unknown origin of some symptoms and pathologies, such as angina pectoris and sudden death.

Limitations and recommendations for future studies. This study analyzed a single sample focusing on the anatomical structures of a 67-year-old patient, which could influence age-related anatomical changes. The use of additional markers and patient samples would be interesting to improve descriptive power in the context of a particular disease.

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RESUMEN: La contracción cardíaca se realiza por estímulos contráctiles del miocardio específico y por regulación simpática y parasimpática, cuyos ganglios se localizan a nivel del mediastino. Este estudio analiza otras vías nerviosas organizadas en unidades ganglionares en el pericardio atrial humano y la grasa parda circundante. Muestras humanas del atrio derecho, obtenidas y autorizadas por la Facultad de Medicina de la Universidad de Chile, se fijaron en formalina al 10 % durante 48 horas (cortes de 5 µm). Para el análisis histológico de las muestras, se utilizaron hematoxilina y eosina de rutina y técnicas especiales de tinción con azul de toluidina, orceína y van Gieson para la observación de cuerpos de Nissl, fibras elásticas, citoplasma, colágeno y grasa parda, respectivamente. Se emplearon técnicas de inmunohistoquímica para reconocer la presencia de neurofilamentos y la proteína S100 (DAB). El análisis histológico e inmunocitoquímico reveló la presencia de un ganglio compuesto por neuronas globosas que reaccionaron positivamente al reconocimiento de neurofilamentos, elementos distintivos del citoesqueleto neuronal. Las células que rodean las neuronas mostraron reacción positiva a proteína S100. Además, se observó grasa parda subepicárdica. El estudio concluye demostrando y describiendo la presencia de ganglios bien constituidos en el tejido conectivo subepicárdico, con una abundante cantidad de grasa parda. La presencia de ganglios y grasa parda podría explicar algunos síntomas y patologías de origen desconocido, como lo son anginapectoral y muerte súbita.

PALABRAS CLAVE: Anatomía; Pericardio; Ganglio; Humano; Grasa cardíaca.

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