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- Sinus of Valsalva aneurysm that fistulizes into the right atrium

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Referencias: 1. Setiawati A, Pohan T. Safety and Effectiveness of Candesartan and Candesartan/HCT Fixed Dose Combination in Patients with Hypertension. *Acta Medica Indonesiana -The Indonesian Journal of Internal Medicine* 2013; 45(3): 193-201. **2.** Bramlage P, Buhck H, Zemmrich C. Candesartan Cilexetil 32 mg/Hydrochlorothiazide 25 mg in Unselected Patients with High or Very High Cardiovascular Risk: Efficacy, Safety, and Metabolic Impact. Springer International Publishing Switzerland 2014: 1-9. **3.** Mugellini A, Nieswandt V. Candesartan plus hydrochlorothiazide: an overview of its use and efficacy. *Expert Opin. Pharmacother* 2012;13(18):2699-2709. **4.** Melian E. B., Jarvis B. Candesartan Cilexetil plus Hydrochlorothiazide Combination. A Review of its Use in Hypertension. *Drugs* 2002; 62 (5): 787-816. **5.** Ohman K.P., Milon H., Valnes K. Efficacy and Tolerability of a Combination Tablet of Candesartan Cilexetil and Hydrochlorothiazide in Insufficiently Controlled Primary Hypertension-Comparison with a Combination of Losartan and Hydrochlorothiazide. *Blood Pressure* 2000; 9: 214-220. **6.** Koenig W. Comparison of the Efficacy and Tolerability of Combination Tablets Containing Candesartan Cilexetil and Hydrochlorothiazide or Losartan and Hydrocllorothiazide in Patients with Moderate to Severe Hypertension Results of the CARLOS-Study1. *Clin Drug Invest* 2000; 19 (4): 239-246. **7.** Scott L. J., McCormack P. L. Olmesartan Medoxomil A Review of its Use in the Management of Hypertension. *Drugs* 2008; 68 (9): 1239-1272. 8. Precio Máximo al Público Junio 2016.

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Referencias: 1. Jones P. H., Davidson M.H., Stein A. E., et al. Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses (STELLAR* Trial). The American Journal of Cardiology 2003; 92: 152-160 **2.** Colivicchi F., Sternhufvud C., Gandhi S. K. Impact of treatment with rosuvastatin and atorvastatin on cardiovascular outcomes: evidence from the Archimedes-simulated clinical trials. ClinicoEconomics and Outcomes Research. 2015; 7: 555-565. **3.** Rehman A. Comparison of Low-Dose Rosuvastatin with Atorvastatin in Lipid-Lowering Efficacy and Safety in a High-Risk Pakistani Cohort: An Open-Label Randomized Trial. Journal of Lipids. 2014: 1-5. **4.** Barakat L., Jayyousi A., Bener A., et al. Comparison of Efficacy and Safety of Rosuvastatin, Atorvastatin and Pravastatin among Dyslipidemic Diabetic Patients. ISRN Pharmacology. 2013: 1-7. **5.** Chustecka Z. Rosuvastatin the most potent statin yet. Heartwire from Medscape. 2000: 1-2. **6.** Yahon C., Chenggong J., Meilin L., et al. Efficacy and safety comparison of different statins in elderly patients. Chin J Cardiol. 2014; 42(11): 910- 915. **7.** Ogawa H., Matsui K., Saito Y., et al. Differences Between Rosuvastatin and Atorvastatin in Lipid-Lowering Action and Effect on Glucose Metabolism in Japanese Hypercholesterolemic Patients With Concurrent Diabetes. Circulation Journal. 2014; 78: 2512-2515. **8.** Scott L. J., Curran M. P., Figgitt D. P. Rosuvastatina, una revisión de su uso en el tratamiento de las dislipidemias. Am J Cardiovasc Drugs. 2004; 4 (2): 117-140. **9.** Adams S., Sekhon SS., Wright JM. Lipid-lowering efficacy of rosuvastatin (Review). The Cochrane Collaboration. Published. 2014; 11: 1-260. **10.** Ulku M. U., Aygul N., Altunkeser B. B., et al. Comparative effects of high-dose atorvastatin versus moderate-dose rosuvastatin on lipid parameters, oxidized-LDL and inflammatory markers in ST elevation myocardial infarction. Atherosclerosis .2015; 239: 439-443. **11.** Fox K.M., Gandhi S.K., Ohsfeldt R.L., et al. Comparison of Low-density Lipoprotein Cholesterol Reduction After Switching Patients on Other Statins to Rosuvastatin or Simvastatin in a Real-world Clinical Practice Setting. The american journal of managed care 2007; 13(10): S270-S275. **12.** Precio Máximo al Público Junio'16.

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Review

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G-proteins coupled receptors

Receptores de membrana acoplados a proteínas G

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INTRODUCTION

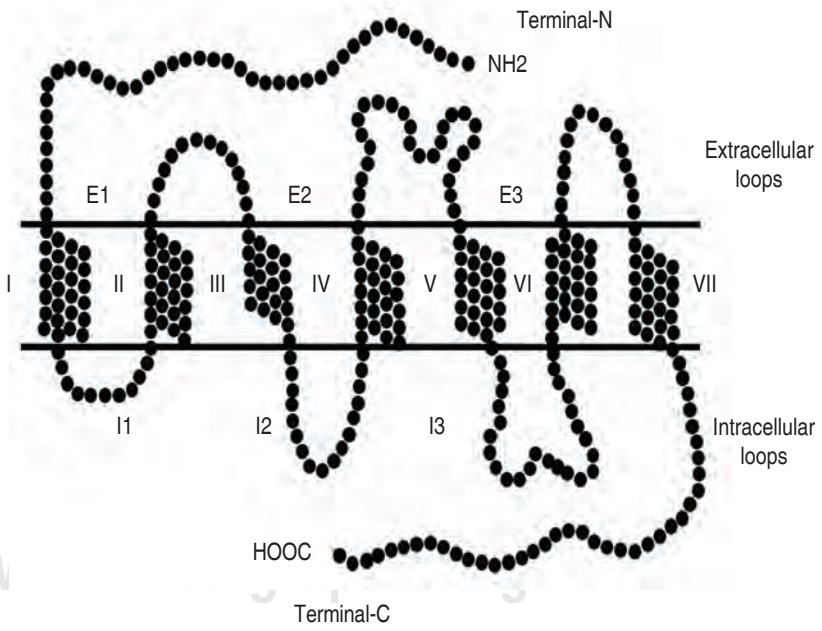
The membrane receptors (GPCRs) coupled to regulatory binding proteins (G proteins), also known as R7G (receptors with 7 transmembrane domains, coupled to guanine nucleotide G proteins *(Figure 1)*, heptahelical or serpentine receptors, form a large and ubiquitous protein superfamily, in charge of fundamental cellular functions.[1-3] In humans, more than 800 of such receptors have been cloned, although a great proportion of them remains orphaned (without known ligand), while many others have been poorly, structurally and functionally, characterized. A wide variety of natural and synthetic molecules (such as hormones, neurotransmitters, autacoids, nutrients, ions, photons, substances involved in odor and taste, and a wide variety of pharmacological agents) exert their stimulatory or inhibitory actions through interaction with these receptors. Examples of these ligands are adrenergic hormones, acetylcholine, serotonin, histamine, adenosine, bradykinin, vasoactive intestinal polypeptide, cannabinoids, opioids, and some pheromones, among many other molecules.[4,5] Under the light of this knowledge, numerous drugs have been designed or have been found to be useful in antagonizing or stimulating these receptors in a variety of clinical conditions, as hypertension, heart failure, obesity, type 2 diabetes mellitus, renal damage, antiplatelet therapy, neurodegenerative diseases (as Alzheimer's, Parkinson's and Huntington's diseases and some forms of vascular and senile dementia), bronchial asthma, macronodular adrenal hyperplasia and adrenal Cushing syndrome, pain and itch, as well as immunity and inflammation, among many other more.[6-15] A great proportion of current approved drugs and others that will be introduced in the near future, target GPCRs, fact that underlines the clinical importance of this receptor family.[3,16]

Clinicians, practical recipients of this basic knowledge, must know more deeply the function and consequences of these agonist/antagonist-receptor relationships, in order to better understand both; the basic molecular mechanisms of some diseases, as well as the mode of action of agonist and antagonist agents in many clinical settings.

Examples of types and actions of GPCRs. The hierarchical structure of GPCR superfamily is rather complex.[3] It is composed by, at least, seven independent families, each of which is categorized in several subfamilies and sub-subfamilies, which are subdivided in turn in a number of subtypes. According with the A-F system of notation,[3] the seven basic families of GPCRs are: class A (rhodopsin like); class B (secretin like); class C (metabotropic glutamate/pheromone, and associated vomeronasal, V1R and V3R, and taste receptors, T2R); class D (the fungal mating pheromone); class E (cyclic AMP, cAMP receptors); class F (the frizzled, FZD, and smoothened, SMO receptors); and finally the adhesion family, which is not identified by any letter in this notation system.[17]

Some of the more abundant and better studied GPCRs, with paramount importance in clinical medicine, pertain to class A. For example, the rhodopsin-like receptors, expressed in retina, are specialized in phototransduction, (the conversion of light in a biochemical cascade signaling to produce vision).[18] The adrenergic receptors, α and β adrenoceptors (the best studied of this superfamily), whose ligands are catecholamines, also belong to this

family. Also belong to class[19] As it is known, adrenergic stimulation is one of the executive branches of the autonomic nervous system, involved in multiple functions related to heart function, arterial tone, nervous reflexes, smooth muscle tone of several structures (ureters, gastrointestinal tube, bronchioles, pregnant uterus, etc.), metabolic actions on insulin and glucagon, increased lipolysis, thermogenesis, renin secretion, brain functions as the handling of sensorial stimuli, memory processing, and other pre-frontal cognitive abilities, among many others. GPCRs of the same class, the muscarinic acetylcholine receptors,[20] mediate the actions of the other autonomic branch, the parasympathetic system, whose actions, in general, are dialectically opposed to those of the adrenergic system. Also to this class A pertain adenosine receptors,[21] responsible of the multiple pleiotropic effects of this autacoid, a precursor of phosphate organic complexes: cyclic adenosine monophosphate (cAMP), adenosine diphosphate, and adenosine triphosphate (ADP and ATP respectively). ATP, as it is known stores and releases the energy produced principally by the three power causeways: the phosphagen system, anaerobic glycolysis (Embden-Meyerhof pathway) and the tandem-like systems of aerobic glycolysis-electron transport chain (Krebs cycle and mitochondrial respiratory chain complex). The lack of oxygen availability during an episode of ischemia, reduces the aerobic production of ATP, diminishing or suppressing Krebs cycle, the most profitable and efficient system of production and storage of energy. A «reverse cascade» then takes place, because secondary to the decrease of ATP production, increases proportionally the accumulation of its precursors, ADP, then AMP and finally, adenosine. The latter, acting on a specific GPCR receptor increase nitric oxygen bioavailability, regulating coronary flow according to metabolic myocardial demands (adenosine hypothesis or Berne & Rubio mechanism),[22] attenuating at the same time myocardial contractility and myocardial oxygen consumption caused by adrenergic stimulation. In addition, adenosine diminishes



GPCRs receptors are characterized by seven α-helical trans-membrane domains (I-VII), three extracellular (E) loops and three intracellular (I) loops. Agonists are nested in sites of the extracellular loops, while intracellular terminal-C is related with the translator G proteins.

Figure 1: Molecular structure of GPCRs.

sinusal activity, slows atrial-ventricular (A-V) conduction, and shortens atrial action potential duration and refractoriness, reducing also ventricular automatism, without influencing His-Purkinje conduction velocity.[23]

Receptors that mediate the action of different members of angiotensin family appertain also to class A GPCRs.[24] The most important are angiotensin II type 1 receptor (AT_1 receptor) and the angiotensin II counter-regulatory type 2 receptor (AT_2).[25] Oncogene mas acts as a putative receptor for angiotensin 1-7, in charge of the most important counter-regulation mechanism of angiotensin II, opposing all systemic and local actions of the latter hormone.[26] Angiotensin II, when it interacts with the AT_1 receptors, causes systemic effects as arteriolar vasoconstriction, lessening of renal flow with increase of intra-glomerular pressure, rise of peripheral resistance and blood pressure, release of hormones like aldosterone and antidiuretic hormone, expansion of intravascular volume, and stimulation of thirst. And also, at local level, the activation of AT_1 receptors, via several signaling pathways give place to a series of beneficial phenomena regulating tissue and vascular defense and repair, but when deregulated impose serious functional and structural damage caused due to proinflammatory, prooxidative, pro-proliferative, prothrombotic and proapoptotic effects.[27]

A little less studied, but arousing a growing interest, are the class B GPCRs,[28] named the secretin family, involved in fundamental functions as glucose homeostasis, via peptide ligands as glucagon, as well as intestinal incretin hormones, glucagon-like peptide (GLP 1 and 2) and glucose-dependent insulinotropic peptide (GIP).[29,30] These peptides, mainly GLP-1, lower blood glucose, stimulating the formation of insulin, via gene transcription, islet cell growth, and neogenesis of β-cells, as well as favoring the hormone secretion. All these actions are carried out by activation of a specific class B GPCR. The enzyme dipeptidyl peptidase 4 (DPP-4) that rapidly inactivates intestinal incretin is inhibited by agents called gliptins (or DPP-4 inhibitors, as sitagliptin, linagliptin and alogliptin), which prolong the biological life of GLP-1, a mechanism that gives them an important place in antidiabetic therapy.[31] In the same way, the analogues of GLP-1 (i.e. exenatide), fulfill the same purpose. Other members of this family are the types 1 and 2 corticotropin releasing factor (CRF) receptors.[32] CRF is their main ligand, activating the production of the adrenocorticotropic hormone (ACTH) in anterior pituitary gland, which in turn stimulates the production of cortisol in the cortex of adrenal glands. As it is well known, cortisol produces a variety of responses to many stressors. CRF acting in its receptor increases adrenergic activity, while parasympathetic decreases. CRF and urocortin,[33] a related peptide ligand, suppress appetite, having the latter much more power in this regard. calcitonin,[34] a thyroid hormone, also a member of this family, regulates calcium homeostasis; inhibiting bone osteoclast activity and increasing at the same time renal calcium excretion. Related peptides are calcitonin gene-related peptide (CGRP) and amylin, with a complex set of functions: renal flow control, glucose homeostasis, inhibition of bone reabsorption, satiety, etc. Other members of this family are the parathyroid hormone receptors involved in calcium and phosphorous metabolism,[35] and the vasoactive intestinal polypeptide (VIP),[36] which despite its name is produced in different parts of the body and has a relaxing effect on smooth muscle of gastrointestinal tract and blood vessels, but also is involved in many other gastrointestinal, biliary and pancreatic functions. Also, VIP serves as a non-adrenergic, non-cholinergic neurotransmitter, regulating many circadian rhythms. Furthermore, it has been discovered that the polypeptide has an important role as regulator of coronary tone and flow, contributing also to heart contractility and rate.

Class C GPCRs (metabotropic glutamate/pheromone receptors)[37] forms a large family composed by metabotropic glutamate (mGlu), gamma-aminobutyric $acid_B$ ($GABA_B$), Ca2+-sensing (CaS), and taste and odor receptors. mGlu receptors intervenes in synaptic transmission and excitability of neuronal cells.[38] Their action could be used therapeutically in a wide set of psychiatric and neurodegenerative disorders.[39] GABA (gamma-aminobutyric acid) is the main

inhibiting neurotransmitter of the central nervous system, weakening the transmission of neural signal. It uses two types of receptor: type A ($GABA_A$) functions as ligand-gated transmembrane ion channels (ionotropic receptors), while type B ($GABA_B$) acts as GPCRs, transmitting their signal via G proteins and a second messenger (metabotropic action). The intracellular actions include inhibition of adenylyl cyclase, which in turn inhibits the voltage-dependent calcium channels, and doing so induces a long-sustained synaptic transmission inhibition, later and slower in comparison with which is caused by type A GABA.[40,41] $GABA_B$ agonism effects can be used in the management of pain, as an inhibitor of nociceptive transmission in afferent fibers, but sufficient clinical evidence is still lacking. These drugs have also promissory evidence in neuropathic pain and spastic disorders. Also, $GABA_B$ agonists have been tested for the treatment of alcohol and cocaine addiction and a series of psychiatric and neurological conditions. CaS (calcium sensing receptor) is a unique GPCR, synthetized in both parathyroid glands and kidneys, whose ligands are Ca^{++} ions. The receptor intervenes in calcium homeostasis regulating the secretion of parathyroid hormone. Allosteric agonists, acting as calcium mimetics have been tested with certain success in various metabolic calcium disorders, as hyperparathyroidism, some kinds of hypocalcemia and osteopenia/osteoporosis.[42]

The vomeronasal organ (VNO) has crucial importance in many inferior animals. Located in the highest part of the nasal septum, serves a detecting organ of pheromones and scent molecules, which in turn yields to multiples effects on animal social, mating, and preying behavior.[43,44] Although it was thought that VNP did not exist at all in humans, there is convincing evidence that shows its existance, although less developed than in lower mammals and reptiles. Unlike what happens in lower animals that have a pair of these organs, in humans, it is usually unilateral, without neural connections.[43,44] Surely, VNO (Jacobson organ) in humans represent a non-operational, fading basic chemical communication system with members of our same species.[44] Notwithstanding, there are some evidences signaling the existence of human pheromones, steroids produced in the skin that can elicit certain sex hormones modifications in men and women.[45] Regarding the savor sense, there are six basic tastes: sweetness, bitterness, *umami* (from the Japanese term *umai* meaning delicious or savory), and the taste of fat caused by the detection of free fatty acids in food («*oleogustus*»), sourness, and saltiness.[46-48] The first four are detected by GPCRs expressed in specialized test cells located in gustatory tongue papillae and other portions of the oropharyngeal cavity.[49] Among taste disorders, are known the absolute absence of taste (ageusia), the reduction of this sense (hypogeusia), the confusion in determining different tastes (dysgeusia), and the permanence of a taste, generally unpleasant, that does not correspond to any meal or substance swallowed (phantom taste).[50] Taste sensing and signaling in mammals, including humans is an extremely complex function. A part of the cluster of chemical signs and receptors involved in this matter, GPCRs are expressed in some type II cells from the bud taste and contribute to the build-up of tasting sense. Taste dysfunction can be observed in a bunch of acute and chronic diseases and conditions, such as viral flu infections, VIH, ageing, diabetes, autoimmune diseases, cancer, nutritional deficiencies, as effects of ionizing radiations, and drugs side-effects, among many others.[50,51] In this regard, antagonists of the AT_1 angiotensin II receptors reduce taste sensitivity by already unclear mechanisms, while the metallic phantom-taste frequently observed with the chronic use of the ACE inhibitor captopril is related to its thiol-group which can form chelated zinc compounds.[52] So far, has not been elucidated the possible involvement of GPCRs Class B and C in taste disorders.

The remaining GPCRs families, class D, E, F and adhesion have been, so far, less studied. D class serves mating responses in fungi,[3] while class E receptors were found in *Dictyostelium discoideum*, a lime mold that can live as a unicellular amoeba, but in certain circumstances can aggregate with other of its own species to form multicellular beings.[53] Class F is composed by Frizzled and Smoothened (SMO) proteins in human beings, playing several roles in cancerogenesis, stem

cells and embryo development.[54,55] Finally, in humans the adhesion family consists of 33 receptors the effects of some members of this family have been related to organogenesis, neurodevelopment, myelination, angiogenesis, and cancer progression.[56]

Structure of GPCRs

GPCR receptors are known as seven transmembrane receptors (7TM), as their common feature is the presence of seven α-helical transmembrane domains (TM 1-7) combined with three extracellular loops and three intracellular loops *(Figure 1)*.[56-59] Specific segments of the extracellular loops are the place where ligands interact with the receptors, while the intracytosolic loops are in contact with G proteins. The external terminus of the peptide chain contains an amide group (NH_2), while the internal has a carboxyl group (COOH). The single polypeptide of many GPCRs has among 290 to 951 aminoacid residues *(Figure 1)*.

Guanine nucleotide-binding proteins (G proteins, GPs) are specialized in signal transducing *(Figure 2)*.[60] A group of them, are heterotrimeric

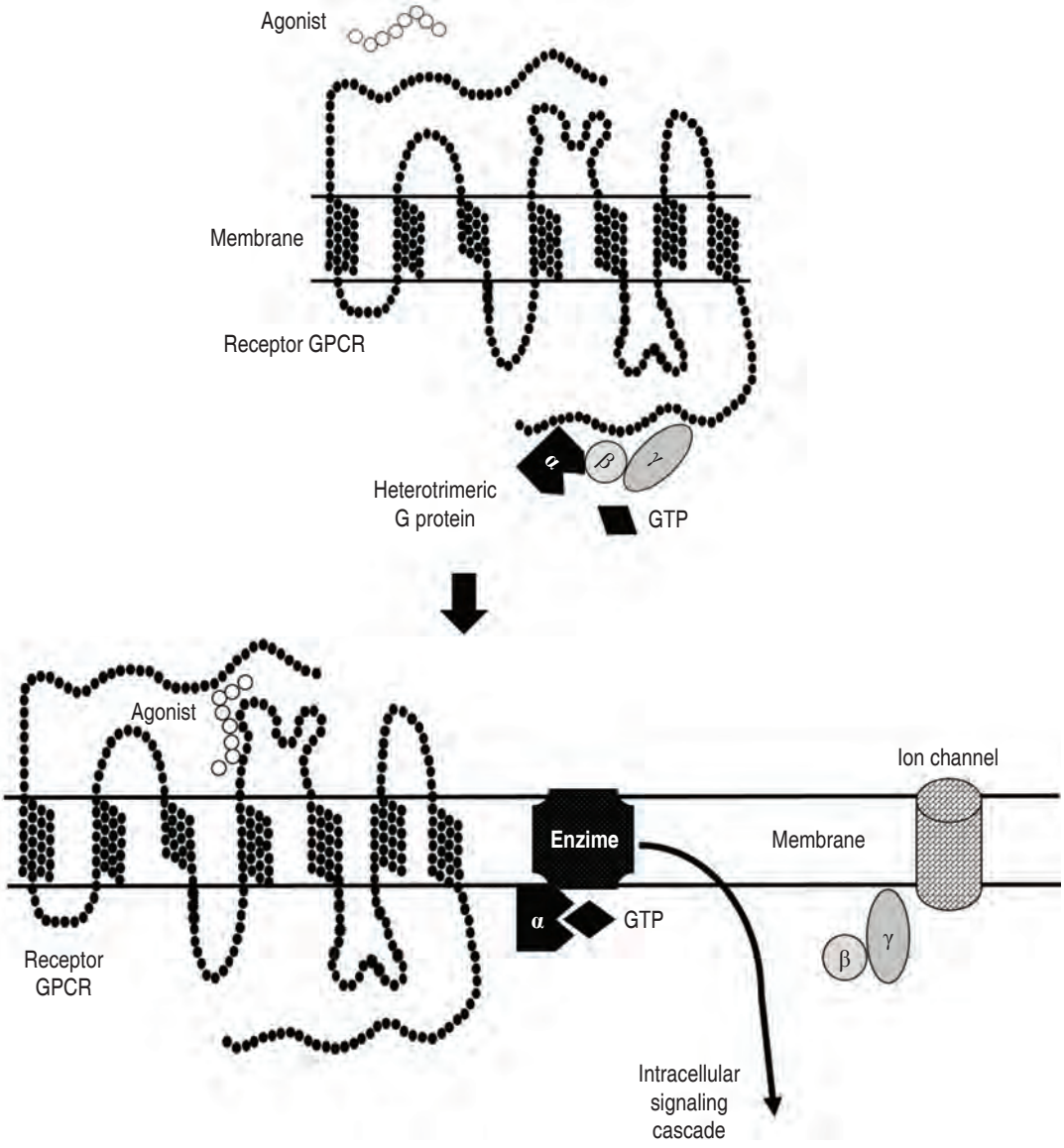


Figure 2:

Function of GPCR receptors.

proteins, i.e., formed by three different structurally independent subunits, named α, β, and γ. G_α contains guanosine triphosphate (GTP),[61] one of the energy transfers formed in the Krebs cycle. G_α is bound to the internal structure of the receptor, as well to a composed unit formed with β and γ subunits. This is the arrangement when the receiver is in an inactivate state. When an agonist nests in the external portion of the receptor, an allosteric change of shape and function of G_α takes place. G_α has GTPase activity, converting GTP in guanine diphosphate (GDP), and releasing energy. By acting in such way, G_α behaves as an activation/deactivation switch of many transducing processes. When GTP is activated, the trimeric structure is broken, but β and γ subunits stay together, and elicit their own intracellular or membrane effects, while liberated G_α can freely interact with other substrates or effectors, in the vicinity of cell membrane, forming molecules who play the role of second messengers in the signaling cascade. Once GTP is converted in GDP, G_α enters in a phase of rest, and the three subunits are reunited, recovering their basal trimeric nature.[57,58]

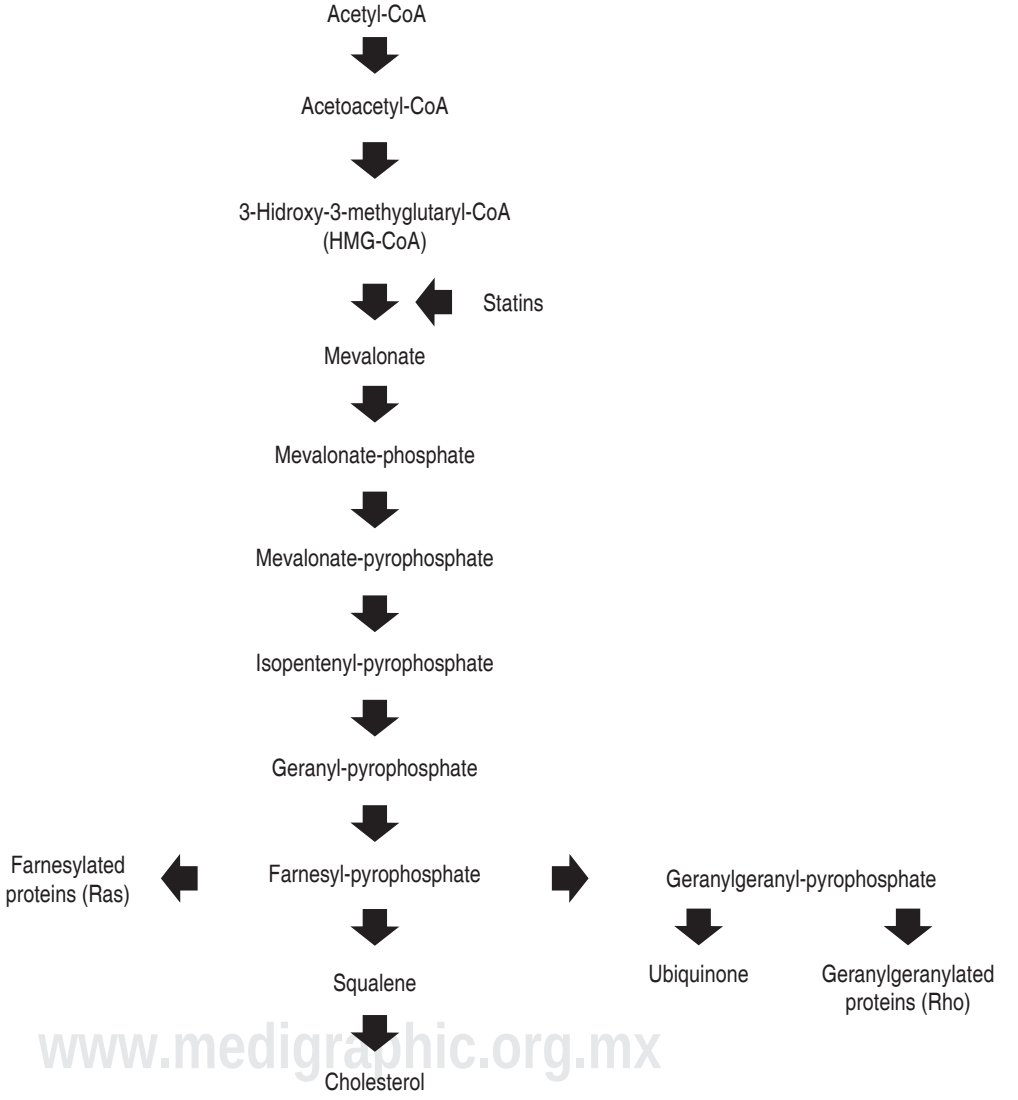
A simplified example of the above is provided by the interaction of angiotensin II with AT_1 receptor *(Figure 2)*.[62] The octapeptide interacts with the extracellular orthosteric binding site, in the loop E2, activating the receptor and initiating a conformational and functional change in G_α. When G_α is freed goes to the membrane and in turn, activates the enzyme phospholipase C (PLC), which among other functions, hydrolyze a constitutive membrane phospholipid, phosphatidylserine, producing two second messengers, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). The former, without leaving the membrane activates protein kinase C (PKC), a multifaceted messenger, which phosphorylating several proteins, exerts a number of functions, among them, muscle contraction and growth (is one of the reasons why angiotensin II is a vasoconstrictor, as well as a growth promoter). On the contrary, IP3 abandon the membrane in which is produced, and reaches the endoplasmic/sarcoplasmic reticulum, and through a specific receptor allows the exit of Ca^{++} to the cytosol, in favor of its osmotic gradient. Ca^{++} has several functions, as facilitating muscle contraction and cell proliferation.

For more complexity, G_α is not a single protein, but indeed form an enter family of different classes. There are varieties of the protein with particular functions, pertaining to several GPCRs. At least are recognized four groups of theses G_α subunits: $G\alpha_s$, $G\alpha_i$, $G\alpha_q$, and $G\alpha_{12}$. For example, $G\alpha_s$ stimulates the enzyme adenylcyclase, forming at the end cAMP, a second messenger involved in multiple signaling processes. On the contrary, $G\alpha_i$, is composed by a large number of inhibitory proteins which inhibits adenylcyclase and reduces the amount of cAMP. $G\alpha_q$ activates PLC, generating the abovementioned second messengers DAG and IP3. Finally, $G\alpha_{12}$ (also called $G\alpha_t$ or transducin), is specialized in photo-transduction in the retina.[63]

There is another family of small monomeric G proteins akin to G_α, which function as GTPases.[64,65] As their similar greater GPs, they behave as binary switches of multiple cellular functions (as cytoskeletal organization, polarity, gene expression, cell differentiation, mobility, lipid endocytic trafficking, etc.)[63] in a cyclic GTP/DGP sequence controlled by regulatory proteins, some of them stimulating GTP formation, while others promoting the conversion to GDP (GDP/GTP-exchange factors and GDP-dissociation inhibitors, respectively). As the bigger GPCRs, small GPs are activated when bound to GTP and become inactivated when GTP switches to GDP. GPs are assembled in large families. Members of the Ras family (the name comes from *rats sarcoma*,[66,67] animal model in which they were discovered) are involved in cell proliferation and cancer genesis (they are oncogenes), although many of them are in fact tumor suppressors. A homologous group, known for that reason as Rho family is also intermingled in a copious amount of cellular processes, mainly, cell morphology and mobility. Other important groups of these small GTPases are Rab, Ran, Miro and Arf families.[65]

An example of the function of these small monomeric molecules is their relationship with the mevalonate cascade, which final product is cholesterol *(Figure 3)*.[68] The rate-limiting step for cholesterol biosynthesis is the activity of the enzyme 3-hidroxi-3-metil-glutaril-CoA reductase

(HMG-CoA), which is inhibited by statins. In this cascade, are produced also intermediate non-sterol metabolites, isoprenoids as isopentenyl pyrophosphate, farnesyl and geranylgeranyl diphosphates (FPP and GGPP), dolichol and ubiquinone. Using specific tranferases, FPP and GGPP attaches farnesyl or geranylgeranyl moieties to the protein to be modified. This posttranslational modification is known as prenylation or farnesylation, which allow small GPs to be attached in the cell lipid membrane, where they can interact with specific receptors, initiating or modulating several signal transduction systems, getting going, for example several phenomena as cell proliferation, differentiation, apoptosis, or cytoskeleton organization.[69] This is the reason why statins, apart from the reduction of *de novo* cholesterol production, exert the so-



The mevalonate pathway leads on one hand to the biosynthesis of de novo cholesterol, but also to the formation of intermediate, non-steroidal metabolites, isoprenoid compounds, whose function is the prenylation or farnesylation of proteins, among them, small monomeric G proteins, involved in in the implementation of many inflammatory, apoptotic, degenerative and proliferative processes.

Figure 3: Generation of small G proteins the mevalonate pathway.

called «pleiotropic» beneficial actions, decreasing the biological effects of small GPs.

CONCLUSION

The GPCR family is involved in many physiologic processes and has a role in numerous biopathological mechanisms of multiple diseases. Currently, a great number of drugs target diverse CGPR, as was discussed in the text. In the near future an even greater number of drugs will be used to inhibit or stimulate these receptors, and induce therapeutic modifications in a variety of pathologies.

The clinician dedicated primarily to the care, diagnosis and treatment of patients will better perform its important missions if it is able to introduce in her or his mental mechanisms the concepts derived from the knowledge of the interaction among agonists and antagonists with the vast variety of receptors that must be considered therapeutic targets.

REFERENCES

1. Rosenbaum DM, Rasmussen SGF, Kobilka BK. The structure and function of G-protein-coupled receptors. Nature. 2009; 459: 356-363.
2. Strosberg AD. Structure/function relationship of proteins belonging to the family of receptors coupled to GTP-binding proteins. Eur J Biochem. 1991; 196: 1-10.
3. Hu GM, Mai TL, Chen CM. Visualizing the GPCR network: Classification and evolution. Scientific Reports. 2017; 7: 15495.
4. Wacker D, Stevens RC, Roth BL. How ligands illuminate GPCR molecular pharmacology. Cell. 2017; 170: 414-427.
5. Katritch V, Cherezov V, Stevens RC. Structure-function of the G-protein-Coupled receptor superfamily. Annu Rev Pharmacol Toxicol. 2013; 53: 531-556.
6. Riddy DM, Delerive P, Summers RJ, Sexton PM, Langmead CJ. G protein-coupled receptors targeting insulin resistance, obesity, and type 2 diabetes mellitus. Pharmacol Rev. 2018; 70: 39-67.
7. Wang J, Gareri C, Rockman HA. G-Protein-coupled receptors in heart disease. Circ Res. 2018; 123: 716-735.
8. Reimann F, Gribble FM. G protein-coupled receptors as new therapeutic targets for type 2 diabetes. Diabetologia. 2016; 59: 229-233.
9. Park F. Activators of G Protein signaling in the kidney. J Pharmacol Exp Ther. 2015; 353: 235-242.
10. Gurbel PA, Kuliopulos A, Tantry US. G-Protein–Coupled receptors signaling pathways in new antiplatelet drug development. Arterioscler Thromb Vasc Biol. 2015; 35: 500-512.
11. Huang Y, Todd N, Thathiah A. The role of GPCRs in neurodegenerative diseases: avenues for therapeutic intervention. Curr Opin Pharmacol. 2017; 32: 96-110.
12. Billington CK, Pen RB. Signaling and regulation of G protein-coupled receptors in airway smooth muscle. Respir Res. 2003; 4: 2.
13. Assie G, Louiset E, Sturm N, René-Corail, F, Groussin L, Bertherat J et al. Systematic analysis of G protein-coupled receptor gene expression in adrenocorticotropin-independent macronodular adrenocortical hyperplasia identifies novel targets for pharmacological control of adrenal Cushing's syndrome. J Clin Endocrinol Metab. 2010; 95: E253-E262.
14. Geppetti P, Veldhuis NA, Lieu TM, Bunnett NW. G Protein-coupled receptors: dynamic machines for signaling pain and itch. Neuron. 2015; 88: 635-649.
15. Lin HH, Hsiao CC, Pabst C, Hébert J, Schöneberg T, Hamann J. Adhesion GPCRs in regulating immune responses and inflammation. Adv Immunol. 2017; 136: 163-201.
16. Hauser AS, Attwood MM, Rask-Andersen M, Schiöth HB, Gloriam DE. Trends in GPCR drug discovery: new agents, targets and indications. Nat Rev Drug Discov. 2017; 16: 829-842.
17. Paavola KJ, Hall RA. Adhesion G protein-coupled receptors: signaling, pharmacology, and mechanisms of activation. Mol Pharmacol. 2012; 82: 777-783.
18. Mustafi D, Palczewski K. Topology of class A G protein-coupled receptors: insights gained from crystal structures of rhodopsins, adrenergic and adenosine receptors. Mol Pharmacol. 2009; 75: 1-12.
19. Ciccarelli M, Sorriento D, Coscioni E, Iaccarino G, Santulli G. Adrenergic receptors. academic press. London UK: Endocrinology of the Heart in Health and Disease: Integrated, Cellular, and Molecular Endocrinology of the Heart; 2009. pp. 285-315.
20. Eglen RM. Muscarinic receptor subtypes in neuronal and non-neuronal cholinergic function. Auton Autacoid Pharmacol. 2006; 26: 219-233.
21. Sheth S, Brito R, Mukherjea D, Rybak LP, Ramkumar V. Adenosine receptors: expression, function and regulation. Int J Mol Sci. 2014; 15: 2024-2052.
22. Berne RM. The role of adenosine in the regulation of coronary blood flow. Circ Res. 1980; 47: 807-813.
23. Lerman BB, Belardinelli L. Cardiac electrophysiology of adenosine. Basic and clinical concepts. Circulation. 1991; 83: 1499-1509.
24. Singh KD, Karnik SS. Angiotensin receptors: structure, function, signaling and clinical applications. J Cell Signal. 2016; 1: 111.
25. Li Y, Li XH, Yuan H. Angiotensin II type-2 receptor-specific effects on the cardiovascular system. Cardiovasc Diagn Ther. 2012; 2: 56-62.
26. Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M. The ACE2/angiotensin-(1-7)/MAS axis of the renin-angiotensin system: Focus on angiotensin-(1-7). Physiol Rev. 2018; 98: 505-553.
27. Lavoie JL, Sigmund CD. Minireview: overview of the renin-angiotensin system--an endocrine and paracrine system. Endocrinology. 2003; 144: 2179-2183.
28. Bortolato A, Doré AS, Hollenstein K, Tehan BG, Mason JS, Marshall FH. Structure of Class B GPCRs: new

horizons for drug discovery. Br J Pharmacol. 2014; 171: 3132-3145.
29. Thorens B. Expression cloning of the pancreatic beta cell receptor for the gluco-incretin hormone glucagon-like peptide 1. Proc Natl Acad Sci USA. 1992; 89: 8641-8645.
30. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: similarities and differences. J Diabetes Investig. 2010; 1: 8-23.
31. MacDonald PE, El-Kholy W, Riedel MJ, Salapatek AMF, Light PE, Wheeler MB. The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. Diabetes. 2002; 51 (suppl 3): S434-S442.
32. Hauger RL, Risbrough V, Brauns O, Dautzenberg FM. Corticotropin releasing factor (CRF) receptor signaling in the central nervous system: new molecular targets. CNS Neurol Disord Drug Targets. 2006; 5: 453-479.
33. Slater PG, Yarur HE, Gysling K. Corticotropin-releasing factor receptors and their interacting proteins: functional consequences. Mol Pharmacol. 2016; 90: 627-632.
34. Masi L, Brandi ML. Calcitonin and calcitonin receptors. Clin Cases Miner Bone Metab. 2007; 4: 117-122.
35. Vilardaga JP, Romero G, Friedman PA, Gardella TJ. Molecular basis of parathyroid hormone receptor signaling and trafficking: a family B GPCR paradigm. Cell Mol Life Sci. 2011; 68: 1-13.
36. Henning RJ, Sawmiller DR. Vasoactive intestinal peptide: cardiovascular effects. Cardiovasc Res. 2001; 49: 27-37.
37. Chun L, Zhang WH, Liu JF. Structure and ligand recognition of class C GPCRs. Acta Pharmacol Sin. 2012; 33: 312-323.
38. Pin JP, Acher F. The metabotropic glutamate receptors: structure, activation mechanism and pharmacology. Curr Drug Targets CNS Neurol Disord. 2002; 1: 297-317.
39. Simeone TA, Sanchez RM, Rho JM. Molecular biology and ontogeny of glutamate receptors in the mammalian central nervous system. J Child Neurol. 2004; 19: 343-360.
40. Rondard P, Goudet C, Kniazeff J, Pin JP, Prezeau L. The complexity of their activation mechanism opens new possibilities for the modulation of mGlu and GABABclass C G protein-coupled receptors. Neuropharmacology. 2011; 60: 82-92.
41. Betke KM, Wells CA, Hamm HE. GPCR mediated regulation of synaptic transmission. Prog Neurobiol. 2012; 96: 304-321.
42. Grupo de estudio CINAREN, Torregrosa JV, Morales E, Díaz JM, Crespo J, Bravo J et al. Cinacalcet en el manejo del hiperparatiroidismo secundario normocalcémico tras el trasplante renal: estudio multicéntrico de un año de seguimiento. Nefrología. 2014; 34: 62-68.
43. Francia S, Pifferi S, Menini A, Tirindelli R. Vomeronasal receptors and signal transduction in the vomeronasal organ of mammals. In: Mucignat-Caretta C, editor. Neurobiology of chemical communication. Chapter 10. Boca Raton (FL): CRC Press/Taylor & Francis; 2014.
44. Meredith M. Human vomeronasal organ function: a critical review of best and worst cases. Chem Sens. 2001; 26: 433-445.
45. Trotier D. Vomeronasal organ and human pheromones. Eur Ann Otorhinolaryngol Head Neck Dis. 2011; 128: 184-190.
46. Sanematsu K, Yoshida R, Shigemura N, Ninomiya Y. Structure, function, and signaling of taste G-protein-coupled receptors. Curr Pharm Biotechnol. 2014; 15: 951-961.
47. Melis M, Tomassini-Barbarossa IT. Taste perception of sweet, sour, salty, bitter, and umami and changes due to l-Arginine supplementation, as a function of genetic ability to taste 6-n-propylthiouracil. Nutrients. 2017; 9: 541.
48. Running CA, Craig BA, Mattes RD. Oleogustus: the unique taste of fat. Chem Senses. 2015; 40: 507-516.
49. Cygankiewicz AI, Maslowska A, Krajewska WM. Molecular basis of taste sense: involvement of GPCR receptors. Crit Rev Food Sci Nutr. 2014; 54 (6): 771-780.
50. Ambaldhage VK, Puttabuddi JH, Nunsavath PN, Tummuru YR. Taste disorders: A review. JIAOMR. 2014; 26: 69-76.
51. Feng P, Huang L, Wang H. Taste bud homeostasis in health, disease, and aging. Chem Senses. 2014; 39: 3-16.
52. Henkin RI. Drug-induced taste and smell disorders. Incidence, mechanisms and management related primarily to treatment of sensory receptor dysfunction. Drug Saf. 1994; 11: 318-377.
53. Prabhua Y, Mondal S, Eichingera L, Noege AA. A GPCR involved in post aggregation events in *Dictyostelium discoideum*. Developl Biol. 2007; 312: 29-43.
54. Basith S, Cui M, Macalino SJY, Park J, Clavio NAB, Kang S et al. Exploring G protein-coupled receptors (GPCRs) ligand space via cheminformatics approaches: Impact on rational drug design. Front Pharmacol. 2018; 9: 128.
55. Wright SC, Kozielewicz P, Kowalski-Jahn M, Petersen J, Bowin CF, Slodkowicz G et al. A conserved molecular switch in class F receptors regulates receptor activation and pathway selection. Nature Communication. 2019; 10: 667.
56. Bjarnadóttir TK, Fredriksson R, Schiöth HB. The adhesion GPCR: a unique of G protein-coupled receptors with important roles in both central and peripheral tissues. Cell Mol. Life Sci. 2007; 64: 2014-2119.
57. Kobilka BK. G protein coupled receptor structure and activation. Biochim Biophys Acta. 2007; 1768: 794-807.
58. Gurevich VV, Gurevich EV. Molecular mechanisms of GPCR signaling: a structural perspective. Int J Mol Sci. 2017; 18: 2519.
59. Rosenbaum DM, Rasmussen SGF, Kobilka BK. The structure and function of G-protein-coupled receptors. Mol Pharmacol. 2012; 82: 777-783.
60. Birnbaumer L. The discovery of signal transduction by G proteins: a personal account and an overview of the initial findings and contributions that led to our present understanding. Biochim Biophys Acta. 2007; 1768 (4): 756-771.
61. Milligan G, Kostenis E. Heterotrimeric G-proteins: a short history. Br J Pharmacol. 2006; 147 (Suppl 1): S46-S55.
62. Griendling KK, Murphy TJ, Alexander RW. Molecular biology of the renin-angiotensin system. Circulation. 1993; 87: 1816-1828.
63. Syrovatkina V, Alegre KO, Dey R, Huang XY. Regulation, signaling and physiological functions of G-proteins. J Mol Biol. 2016; 428: 3850-3868.
64. Heider D, Hauke S, Pyka M, Kessler D. Insights into the classification of small GTPases. Adv Appl Bioinforma Chem. 2010; 3: 15-24.

65. Song S, Cong W, Zhou S, Shi Y, Dai W, Zhang H et al. Small GTPases: structure, biological function and its interaction with nanoparticles. Asian J Pharm Sci. 2019; 14: 30-39.
66. Wennerberg K, Rossman KL, Der CJ. The Ras superfamily at a glance. J Cell Sci. 2005; 118: 843-846.
67. Colicelli J. Human RAS superfamily proteins and related GTPases. Sci STKE. 2004; (250): RE13.
68. Hashemi M, Hoshyar R, Ande SR, Chen QM, Solomon C, Zuse A et al. Mevalonate cascade and its regulation in cholesterol metabolism in different tissues in health and disease. Curr Mol Pharmacol. 2017; 10: 13-26.
69. Alizadeh J, Zeki AA, Mirzae N, Tewary S, Moghadam AR, Glogowska A et al. Mevalonate cascade inhibition by simvastatin induces the intrinsic apoptosis pathway via depletion of isoprenoids in tumor cells. Scientific Reports. 2017; 7: 44841.

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Clinical case

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A case never reported before: bilateral type A interruption in a double aortic arch without persistent ductus arteriosus

Un caso nunca antes reportado: interrupción bilateral de tipo A en un arco aórtico doble sin ductus arteriosus persistente

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Lucía Gordillo-Tobar,** Jaime Pinto-León***

Keywords:
Double aortic arch, interrupted aortic arch, persistent ductus arteriosus.

Palabras clave:
Doble arco aórtico, interrupción del arco aórtico, ductus arteriosus persistente.

ABSTRACT

We present the case of a four years seven-month-old patient referred to cardiologist for heart murmur. Echocardiography study revealed interruption of the aortic arch. Magnetic resonance imaging revealed type A bilateral interruption in double aortic arch, with obliterated ductus arteriosus, without septal defect, with collateral network made of two thick anastomotic arteries that join the subclavian arteries to the descending aorta. We haven't found this pathology reported in any medical literature. Asymptomatic patient received control as outpatient in Cardiology Department. Reexamined ten years later with multislice angiotomography, confirming the diagnosis.

RESUMEN

Paciente de cuatro años siete meses que es enviado a Cardiología, por encontrarse un soplo a la auscultación cardíaca. En el estudio ecocardiográfico se le diagnosticó interrupción del arco aórtico. Se estudia al paciente con Imágenes de resonancia magnética, encontrándose una interrupción bilateral Tipo A en un doble arco aórtico, con ductus arteriosus obliterado, sin defectos septales, con una red colateral formada por dos gruesas arterias anastomóticas que unen las arterias subclavias con la aorta descendente. El paciente asintomático es controlado en consulta externa de Cardiología. El paciente es reestudiado diez años más tarde con angiotomografía multicorte, confirmándose el diagnóstico.

INTRODUCTION

Interruption of the aortic arch is a rare congenital malformation, in which the luminal continuity between the proximal aorta and the descending aorta is lost.[1] The first description of this pathology was made by Steidele in 1778.[2] It is a rare pathology, representing less than 1.5% of all congenital heart diseases.[3]

Interruptions of the aortic arch are associated in 98% of cases with persistent ductus arteriosus, and in 90% of cases with interventricular communication,[4] less frequently with subaortic stenosis, transposition of large vessels, and with double outlet right ventricle.[5]

Celoria and Patton[6] classify interrupted aortic arches according to the site of interruption, in three types: type A, when the interruption is found distal from the origin of the left subclavian artery; type B, when it is located between the left carotid artery and the left subclavian artery; and type C, when it is located after the origin of the innominate artery. The most frequent type is B, then A.

Mollers and Edwards[5] refine this classification, creating subtypes according to the origin of the right subclavian artery.

- **Type I.** Interruption is located after the origin of left subclavian artery. Subtype a: right subclavian artery arises from innominate artery; and Subtype b: right subclavian artery arises from descending aorta, becoming an aberrant right subclavian artery.

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- **Type II.** Interruption after left carotid artery. Subtype a: right subclavian artery arises from innominate artery; Subtype b: right subclavian artery arises from descending aorta; and Subtype c: right subclavian artery arises from right pulmonary artery, becoming an isolated right subclavian artery.
- **Type III.** Interruption located after the origin to innominate artery.

When the interrupted aortic arch is accompanied by a persistent ductus arteriosus and interventricular communication, most of the arterial blood flows from the left ventricle to the right ventricle through the septal defect, and from the pulmonary artery to the descending aorta through the persistent ductus arteriosus. The birth of a child with this type of interruption constitutes a surgical emergency, because it is a ductal-dependent pathology. The physiological closure of the duct leads to heart failure, metabolic acidosis, and death. The therapeutic plan to save these children consists in treating the heart failure, infusing prostaglandin E1 to prevent the closure of the duct, and corrective surgery as soon as possible.[7,8]

Three percent of interruptions of the aortic arch[4] happen without persistent ductus arteriosus and without interventricular defect. The first case of this variant was reported by Pillsbury[9] in 1964, in a 16-year-old girl with type C aortic interruption. Afterwards, in 1967 Zetterqvist[10] reported the second case, and in 1970 Morgan[11] reported a third case. In a review of 105 cases of interruptions of the aortic arch, Moller[4] found only two cases with obliterated ductus arteriosus and without septal defect. Some authors have called this type of interruption «complete interrupted aortic arch»,[12,13] «adult-type interruption»,[12] «Solitary Interruption of the Aortic Arch»,[14] «isolated interrupted aortic arch».[15]

Patients with interruptions of the aortic arch without persistent ductus arteriosus and without interventricular communication make up a special group of patients with an entirely different behavior than patients with interruptions of the aortic arch with persistent ductus arteriosus. Dische[14] finds that these patients have a longer survival rate, are diagnosed later in life, the clinical course is more benign, there are fewer complications, and the surgical treatment is more successful.[4,15]

In 1948, Edwards[16] described two types of double aortic arch: type 1, with two arches, both the right and the left arches being totally patent; and type 2, where the right arch is patent, but the left has some degree of atresia or interruption. Shuford in 1971[17] proposed a classification of the interruptions of the left arch in double aortic arches. Type A, located after the ductus arteriosus; type B, after the left subclavian artery; type C, between the common left carotid artery and the left subclavian artery; and type D, before the left common carotid artery. The type C interruption of the left arch creates an aortic arch very similar to the circumflex right aortic arch,[18,19] also called right aortic arch with retroesophageal component and aberrant left subclavian artery, for practical purposes the angiographic features of both anomalies are similar.[18] We have not found in the literature descriptions of bilateral interruptions in double aortic arches.

PRESENTATION OF THE CASE

We present the case of a four years seven months old male, first child, without significant prenatal or family medical history, normal height-weight and psychomotor development. Referred to cardiology by pediatrician who detected heart murmur.

Physical examination: weight 15.6 kg (50^{th} percentile), height 104 cm (50^{th} percentile). The fascies was normal, and no palate anomalies were found. Blood pressure: right arm: 90/60, left arm: 90/60, lower limbs 85/60. Saturation in four limbs: 91%. Cardiac auscultation: rhythmic and normophonetic sounds, holosystolic murmur of intensity 2+/6 in tricuspid foci, without irradiation.

Electrocardiogram: right ventricular hypertrophy. Chest X-ray: heart of normal shape and size.

Echocardiography: prominent left ventricle, mild failure of tricuspid valve. Probable interruption of aortic arch.

Magnetic resonance angiography (MRA): *Situs solitus* with levocardia, atrial-ventricular and ventricular-arterial concordance, integrity of interatrial and interventricular septum, normal drainage of systemic and pulmonary veins.

The 3D volumetric reconstruction images of the contrast-enhanced MRA *(Figure 1 A-C)* reveal a double aortic arch with interruption of the two arches after the origin of the subclavian arteries, presence of two thick anastomotic tortuous arteries arising from posterior aspect of the subclavian arteries and traveling back and down to join the descending aorta, which presents a diverticular formation in its upper end.

MRA diagnosis: bilateral type A interruption in a double aortic arch (according to Celoria's classification), with obliterated arterial duct, without interventricular communication.

Asymptomatic patient undergoes periodical controls in Cardiology Department.

After 10 years, patient is re-evaluated, by then he is 14 years, 7 months old, weight 57 kg (p57), height 150 cm (p5), blood pressure is 110/60 in upper limbs and 90/60 in lower limbs, saturation 91%.

Electrocardiography: right ventricular hypertrophy.

Multi-detector computed tomography angiography (MDCTA) is conducted. The 3D volumetric reconstruction images *(Figure 2 A and B)* show with more detail the findings of the MRA performed 10 years before. The two collateral vessels have a mean diameter of 10 mm and present a short extra-thoracic pathway located behind the third costal arches *(Figure 2C)*.

The current echocardiogram shows visceral *situs solitus*, prominent right chambers with tricuspid morphology similar to Ebstein's anomaly with mild insufficiency.

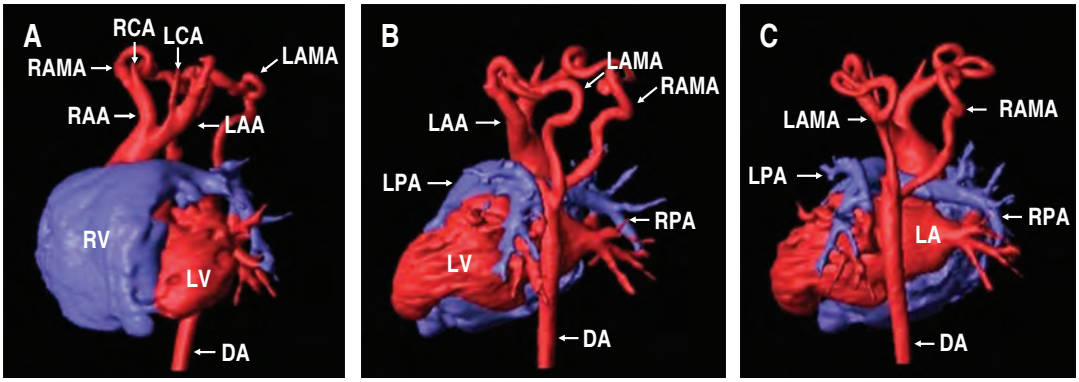
Patient is asymptomatic, has not undergone surgery.

DISCUSSION

We present the case of a patient that, at age 4, was diagnosed with type A bilateral interruption of double aortic arch, without persistent ductus arteriosus and without septal defect.

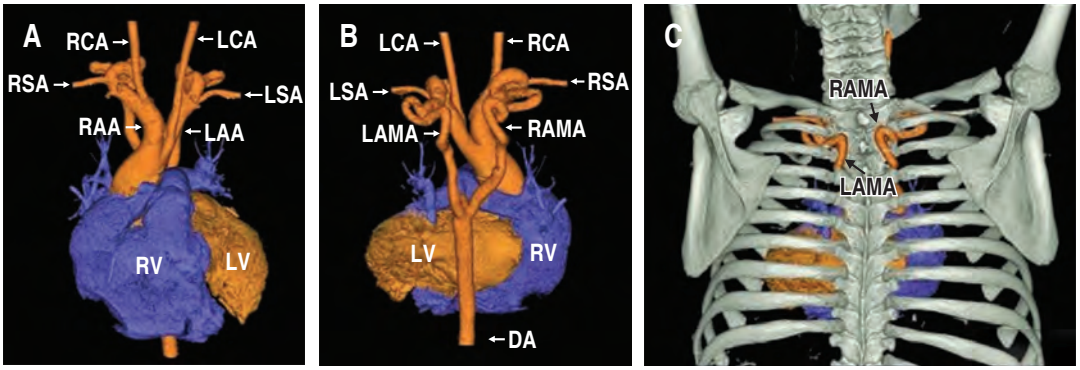
There are two classifications of interruptions of the aortic arch according to the site: Celoria and Patton[6] classify the interruptions in the single aortic arches and Shuford[17] classifies the interruptions of the left aortic arch in double aortic arches. Our patient has a double aortic arch but with bilateral interruption. We have arbitrarily chosen Celoria's classification to call it «type A bilateral interruption», which means that the interruption is found in both arches, after the origin of the subclavian arteries. We have found no reports of similar cases in the medical literature.

Depending on the presence of persistent ductus arteriosus, the interruptions of the aortic arches can also be classified in interruptions with persistent ductus arteriosus and interruptions without persistent ductus



DA = Descending aorta, LA = Left atrium, LAA = Left aortic arch, LAMA = Left anastomotic mediastinal artery, LPA = Left pulmonary artery, LV = Left ventricle, RAA = Right aortic arch, RAMA = Right anastomotic mediastinal artery, RCA = Right carotid artery, RPA = Right pulmonary artery, RV = Right ventricle.

Figure 1: Magnetic resonance angiography when patient was four years, seven months old. 3D volumetric reconstruction images. **A)** Anterior view; **B)** Left lateral view; **C)** Posterior view.

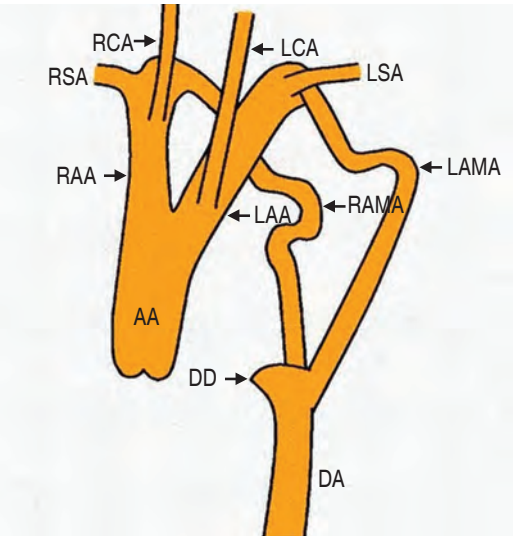


LAA = Left aortic arch, LAMA = Left anastomotic mediastinal artery, LCA = Left carotid artery, LSA = Left subclavian artery, RAA = Right aortic arch, RAMA = Right anastomotic mediastinal artery, RCA = Right carotid artery, RSA = Right subclavian artery.

Figure 2: Contrasted multidetector computerized tomography. 3D Volumetric Reconstruction Images. **A)** Anterior view; **B)** Posterior view; **C)** Posterior view of 3D volumetric reconstruction of heart, vessels and thoracic cage. Observe in **C** the extrathoracic pathway of RAMA and LAMA behind third costal arches.

arteriosus. Interruptions accompanied by persistent ductus arteriosus correspond to 97% of the cases they are diagnosed early during childhood, constitute a surgical emergency, because they are ductal-dependent, and when the ductus arteriosus closes the patients die. While, interruptions of the aortic arch that occur in not accompanied by persistent ductus arteriosus occur in less than 3%,[4] are diagnosed later, often in adults, are more benign and have fewer complications. The case we report belongs to the second group, the patient has obliterated ductus arteriosus, no septal defect, was diagnosed at age 4, is practically asymptomatic, at present he is 14 years old and in good health. He has the characteristics of what Dische[14] calls «solitary interrupted aortic arch».

It has been confirmed that when children are born with an interruption of the aortic arch with persistent ductus arteriosus, they lack a collateral network between the ascending and descending aortas; that is why when the ductus arteriosus closes a catastrophe ensues. Children whose ductus arteriosus is obliterated in utero have time to develop collateral vessels. The same happens with children born with extreme aortic coarctations. Children born with type B and C interruptions of aortic arches[10-13,20] with obliterated ductus arteriosus develop intracranial collateral networks between the arteries arising from the ascending aorta and those arising from the descending aorta. In children born with type A interruptions of the aortic arch with obliterated ductus arteriosus, where the interruption is located after the origin of the left subclavian artery, as in the case we report, all the supra-aortic arteries arise from the ascending aorta, none from the descending aorta, which means that the intracranial anastomotic networks cannot be created, the only possibility is the creation of thoracic and thoraco-abdominal collateral networks. Among the thoracic collateral networks, one of the most important is the one described by Kirks in extreme aortic coarctations[21] as anastomotic mediastinal arteries, formed by the anastamosis of the upper intercostal artery, a branch of the subclavian artery, and the third intercostal arteries, branches of the descending aorta, this is the type of anastomotic arteries our patient has *(Figure 3)*. In the images of the volumetric reconstruction of the MRA *(Figure 1 A-C)*, as well as in the MDCA *(Figure 2 A and B)*, we see two thick and tortuous anastomotic arteries, which connect the subclavian arteries to the descending aorta, with a short extra-thoracic pathway behind the third costal arches *(Figure 2C)*. These mediastinal anastomotic arteries have a mean diameter of 10 mm, capable of carrying an adequate blood flow to the descending aorta and the lower limbs. Blackford,[22] in a case of extreme aortic



AA = Ascending aorta, DA = Descending aorta, DD = Ductus diverticulum, LAA = Left aortic arch, LAMA = Left anastomotic mediastinal artery, LCA = Left carotid artery, LSA = Left subclavian artery, RAA = Right aortic arch, RAMA = Right anastomotic mediastinal artery, RCA = Right carotid artery, RSA = Right subclavian artery.

Figure 3: Schematic drawing of double aortic arch with bilateral interruption after origin of subclavian arteries, presence of two thick mediastinal anastomotic arteries that join subclavian arteries to descending aorta.

coarctation, describes an anastomotic artery similar to the one in our case, between the costocervical trunk and the descending aorta, which had a diameter of 14 mm.

In the upper end of the descending aorta *(Figure 3)* we see a saccular dilatation ending in a cul-de-sac and joining the pulmonary artery: this is a ductal diverticulum,[23] the remnants of the ductus arteriosus obliterated during fetal life.

Cases of interruption of the aortic arch, published in the medical literature, have been diagnosed traditionally using echocardiography and angiography with catheterization,[5,9,11,12,14,24,25] others with magnetic resonance imaging[15,26,27] and some with CTA.[10,20,28] In our hospital we prefer to study cardiopathies and vascular rings in children using magnetic resonance and in adults using multidetector computerized tomography. Our patient was studied with magnetic resonance when he was four years, seven months old, and with multidetector computerized tomography, ten years later. We have not found in the medical literature another case studied with the two imaging modalities.

CONCLUSION

This is an exceptional case of a bilateral interruption in a double aortic arch, with obliterated arterial ductus, causing the intrauterine development of two thick anastomotic arteries, which allowed the asymptomatic growth of the child. We haven't found any similar case reported in medical literature.

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REFERENCES

1. Backer CL, Mavroudis C. Congenital heart surgery nomenclature and database project: persistent ductus arteriosus, coarctation of the aorta, interrupted aortic arch. Ann Thorac Surg. 2000; 69: 298-307.
2. Steidele RJ. Samming. Verschiedener in der chirurgie. Prakt. Lehrschule Gemachten Beobb. 2: 114: 1777-1778.
3. Collins-Nakai RL, Macdonald D, Parisi-Buckley L, Fyler DC, Castaneda AR. Interrupted aortic arch in infancy. J Pediatr. 1976; 88 (6): 959-962.
4. Reardon MJ, Hallman GL, Cooley DA. Interrupted aortic arch: brief review and summary of an eighteen-year experience. Tex Heart Inst J. 1964; 11 (5): 250-259.
5. Moller JH, Edwards JE. Interruption of aortic arch. anatomical patterns and associated cardiac malformations. AJR. 1965; 95 (3): 557-572.
6. Celoria GC, Patton RB. Congenital absence of the aortic arch. Am Heart J. 1959; 58 (3): 407-413.
7. Heymann MA, Berman W, Rudolph AM, Whitman V. Dilatation of the ductus arteriosus by prostaglandin E1 in aortic arch abnormalities. Circulation. 1979; 59 (1): 169-173.
8. Zahka KG, Roland JM, Cutilleta AF, Kidd L. Management of aortic arch interruption with prostaglandin E_1 infusion and a microporous expanded polytetrafluoroethylene grafts. The American Journal of Cardiology. 1980; 46: 1001-1005.
9. Pillsbury RC, Lower RR, Shumway NE. Atresia of the aortic arch. Circulation. 1964; 30: 749-754.

10. Zetterqvist B. Atypical coarctation of the aorta with bilateral vertebral-subclavian pathway. Scand J Thor Cardiovasc Surg. 1967; 1: 6875.
11. Morgan JR, Forker AD, Fosburg, RG, Neugebauer MK Rogers AK, Bemiller CR. Interruption of the aortic arch without a persistent ductus arteriosus. Circulation. 1970; 17: 961-965.
12. Sharrat GP, Carson P, Sanderson JM. Complete interruption of aortic arch, without persistent ductus arteriosus, in an adult. Br Heart J. 1975; 37: 221-224.
13. Kauff MK, Bloch J, Baltaxe HA. Complete interrupted aortic arch in adults. Radiology. 1973; 106: 53-57.
14. Dische MR, Tsai M, Baltaxe HA. Solitary interruption of the arch of the aorta, clinicopathologic review of eight cases. The Am J Cardiol. 1975; 35: 271-277.
15. Messner G, Reul GJ, Flamm SD, Gregoric ID, Opfermann UT. Interrupted aortic arch in an adult. Tex Heart Inst J. 2002; 29: 118-121.
16. Edwards JE. Anomalies of the derivatives of the aortic arch system. Med Clin North Am. 1948; 32: 925-949.
17. Shuford WH, Sybers RG, Weens HS. The angiographic features of double aortic arch. AJR. 1972; 116 (1): 125-140.
18. Garti IJ, Aygen MM, Vidne B. Type C double aortic arch. double aortic arch with aberrant left subclavian artery. Cardiovasc. Radiol. 1975; 1: 143-145.
19. Adachi I, Krishnamurthy R, Morales DL. A double aortic arch mimicking a right aortic arch with an aberrant left subclavian artery. J Vasc Surg 2011; 54: 1151-1153.
20. Cazavet A, Seguela PE, Acar P, Leobon B. A new type of aortic arch interruption without significant persistent ductus arteriosus and with no ventricular septal defect. J Thorac Cardiovasc Surg. 2012; 143: 237-239.
21. Kirks DR, Currarino G, Chen JT. Mediastinal collateral arteries: important vessels in coarctation of the aorta. AJR. 1986; 146: 754-762.
22. Blackford LM. Coarctation of the aorta. Arch Intern Med. 1928; 41:702-735.
23. Salomonowitz E, Edwards JE, Castaneda-Zuniga WR et al. The tree types of aortic diverticula. AJR. 1984; 142: 673-679.
24. Mauck HP, Youker J, Lester RG, Martin C, McCue C. Complete interruption of the aortic arch. Diagnosis by left atrial cardioangiography. Angiology. 1973; 14 (4): 362-367.
25. Losman JG, Joffe HS, Beck W, Barnard C. Successful total repair of interrupted aortic arch associated with ventricular septal defect and large persistent ductus arteriosus. Am J Cardiol. 1974; 33: 566-571.
26. Dillman JR, Yarram SG, D'Amico AR, Hernandez RJ. Interrupted aortic arch: spectrum of MRI findings. AJR. 2008; 190: 1467-1474.
27. Yoo SJ, Choi HY, Park IS, Hong CY, Song MG. Kim SH. Distal aortopulmonary window with aortic origin of the right pulmonary artery and interruption of the aortic arch (berry syndrome) diagnosis by MR Imaging. AJR. 1991; 159: 835-836.
28. Rodríguez PA, Vázquez SM, Mendieta AG, Ávila RL, Ledesma RR, Ortiz AJ, Reza HA. Interrupción del arco aórtico. Arch Inv Mat Inf. 2010; 2 (1): 8-10.

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Non-hyperacute synchronous cardio-cerebral infarction treated by double intervensionist therapy

Infarto sincrónico cardio-cerebral no hiperagudo tratado con doble terapia intervencionista

Juan Carlos Plata-Corona,* José Aurelio Cerón-Morales,** Beatriz Lara-Solís***

Keywords: Acute myocardial infarction, acute ischemic stroke, thrombolysis, thrombectomy, cardio-cerebral infarction.

Palabras clave: *Infarto agudo al miocardio, evento vascular cerebral isquémico, trombólisis, trombectomía, infarto cardiocerebral.*

ABSTRACT

Introduction: The simultaneous appearance of the acute myocardial infarction (AMI) and acute ischemic stroke (AIS) is known as cardio-cerebral infarction (CCI); this condition is extremely rare, and thus complex to treat. There is normally a subjacent cause that triggers these two events to occur simultaneously. Nonetheless, the timely recognition of these conditions is challenging and most of the times is only confirmed by an autopsy. **Objectives:** This article investigates the epidemiology, the physiopathology and the treatment of CCI within the existing literature. **Clinical case:** A 46-years-old male, who is diagnosed of CCI after 5 hours his clinical condition starts. We decided to carry out a double percutaneous approach; intra-arterial thrombolysis plus mechanical thrombectomy of the middle-right cerebral artery (MRCA) was performed, in addition to this, a coronariography with angioplasty and stenting in the proximal segment of the left anterior descending artery (LAD). **Results:** The patient's clinical recuperation was fast and favorable, discharged on the third day without any registry of cardiac failure and a modified Rankin score (mRS) of 2, and 0 at one month. **Conclusion:** CCI is a clinical case very uncommon and generally devastating. Further information is needed to establish an ideal treatment strategy that may lead to better results. Nonetheless, the rarity of the condition makes it difficult to perform clinical trials. Based on the results obtained in this particular case, a combined endovascular approach is suggested in patients with non-hyperacute synchronous CCI.

RESUMEN

Introducción: *La aparición simultánea de infarto agudo de miocardio y evento vascular cerebral isquémico es conocida como infarto cardiocerebral (ICC), esta asociación es extremadamente infrecuente y representa un escenario complejo de cara al tratamiento. En estos casos generalmente hay una causa subyacente que vincula ambos eventos trombóticos. El reconocimiento simultáneo de estas dos condiciones es difícil en términos clínicos, y en muchos de los casos se llega a demostrar únicamente mediante autopsia.* ***Objetivos:*** *En la presente revisión se aborda la epidemiología, fisiopatología y el tratamiento del ICC dentro de la literatura actual.* ***Caso clínico:*** *Masculino de 46 años, diagnosticado de ICC después de cinco horas de iniciado su cuadro clínico, decidimos realizar un doble abordaje percutáneo con trombólisis intraarterial más trombectomía mecánica de la arteria cerebral media derecha asociada a coronariografía con angioplastia y colocación de stent en el segmento proximal de la arteria descendente anterior.* ***Resultados:*** *La recuperación del paciente fue favorable, egresándose al tercer día sin datos de falla cardiaca y con Rankin score modificado de 2, y de 0 al mes.* ***Conclusión:*** *El ICC es poco común y con frecuencia devastador. Se necesitan más estudios para establecer estrategias adecuadas de tratamiento, sin embargo, la rareza de esta condición hace difícil establecer ensayos clínicos para su estudio. Basados en los resultados obtenidos en este caso en particular, sugerimos un abordaje endovascular combinado en pacientes con ICC sincrónico no hiperagudo.*

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INTRODUCTION

AMI and AIS represent the main causes of mortality worldwide. They usually share the same risk factors and pathogenic mechanism. Cardio-cerebral infarction, a term introduced by Omar et al. in 2010, was used to describe the simultaneous occurrence of AIS and AMI. This event is very rare and presents a diagnostic and therapeutic challenge.[1,2]

CCI can be diagnosed by the presence of acute onset of a focal neurological deficit

which suggest AIS, associated to chest pain or evidence of myocardial infarction such as electrocardiogram changes and the elevation of cardiac enzymes.[3,4]

AIS and AMI are both life-threatening medical conditions with narrow therapeutic time-window that carry grave prognosis if not addressed promptly, in this way exist a similarity between the heart and the brain; the time of restoration of blood flow represents a critical moment. Several studies have shown that the effectiveness of any therapy is time dependent. Rapid reperfusion stops the progress of necrosis and preserves viable tissue.

A delayed intervention of one infarcted territory for the other may result in permanent irreversible morbidity or disability of the infarcted area that received delayed intervention.[2]

CCI can be classified as «synchronous» which is a simultaneous infarction in the cerebral and coronary vascular territories, and «metachronous» which is one event preceding the other.[4] In this article, only the synchronous presentation will be described.

Recently, the term «hyperacute» CCI has been proposed to describe patients with CCI who arrived at the hospital within 4.5 hours of the thrombolytic therapeutic window. Patients who present symptoms for more than 4.5 hours are in a non-hyperacute state and cannot receive thrombolytic therapy for the treatment of AIS.[5]

AIS and AMI association was recognized some decades ago and over the years, the awareness of this rare combination has increased. The acute management of both conditions separately is well documented in the literature, however, in case of synchronous presentation, there are no clear recommendations for ideal treatment.

Epidemiology

Chin et al. reported the incidence of metachronous CCI as 12.7% in geriatric patients who were screened for AMI within 72 hours of admission for AIS. Findings from the Global Registry of Acute Coronary Event (GRACE) trial reported an incidence of in-hospital stroke as 0.9% in a cohort of patients presenting with acute coronary syndrome, and the incidence was much higher in patients with S-T elevation Myocardial Infarction (STEMI) than the non-ST elevation.[2,6]

Although there is an increased risk of AMI following AIS and vice versa, CCI has rarely been reported, with a global incidence of 0.009%.[4]

According to the Austrian stroke unit registry, during treatment in the stroke unit (median duration three days), 1% of patients with transient ischemic attack or ischemic stroke and 0.3% of patients with hemorrhagic stroke suffered AMI.[7]

A prospective observational study by Mochmann et al. revealed that approximately 13.7% of patients with acute ischemic stroke had elevated level of cardiac troponin.[8]

Etiology

Pathophysiology of CCI can be classified into three categories: (1) conditions leading to concurrent cerebral–coronary infarction, (2) cardiac conditions leading to cerebral infarction, and (3) brain–heart axis dysregulation or cerebral infarction leading to myocardial infarction. Some conditions that lead to simultaneous AIS and AMI are reported below *(Table 1)*.[5]

Current treatment of cardiocerebral infarction

There are no clinical trials that have addressed this dilemma likely due to its rarity, and there are also no evidenced-based guidelines on the sequence of approach to management. Intravenous thrombolysis with Alteplase (rt-PA), approved for the acute management of both conditions has been suggested as the best approach to the treatment of CCI if there is no contraindication, and both presentations are within the time frame for the administration of a thrombolytic.[2]

We need to remember that in patients with AIS the use of intravenous thrombolysis (a therapeutic option for both vascular territories) is contraindicated if there is a history of AMI in the previous three months.[24] However, this recommendation (class IIb; Level of evidence C) is not evidenced-based and the American Heart Association/American Stroke Association recommend further study of these circumstances.[24,25] Despite the fact that several studies have reported higher risk of cardiac rupture with thrombolytic therapy, with only

1% incidence.[26,27] We need to keep in mind the benefits and risks at the time of choose the best treatment option.

On the other hand, it is known that AMI treated with thrombolysis increases the risk for hemorrhagic conversion of AIS, which represents the worst complication of this approach. Antiplatelet therapy, GP IIb/IIIa inhibitors and anticoagulants used in coronary intervention for AMI also increase the risk of intracerebral bleeding.[28]

Although there are still not enough clinical trials to approve thrombolytic therapy to treat CCI, we consider that treatment with thrombolytic therapy for both vascular territories is a reasonable option when patient present STEMI and AIS within the time frame (<4.5 hours).

Thrombolytic dose, duration and method of administration and time frame for initiating therapy in case of AIS, STEMI, and Pulmonary Embolism (PE) are well described *(Table 2)*, however, there's not exist the adequate dose and duration to treat CCI.[29]

The lack of a clear guideline on the unifying dose for CCI is a source of great controversy

Table 1: Conditions that lead to cardio-cerebral infarction.

Reduced left ventricular systolic function	Anterior and apical wall infarction associated with reduced left ventricular systolic function provides a substrate for the formation of left ventricular mural thrombus.[9] These post AMI thrombi are particularly prone to increased risk of embolization, and may explain CCI[9-11]
Atrial fibrillation	Atrial fibrillation has been reported as a cause of CCI due to common source of both cerebral and coronary embolism[12]
Paradoxical embolism	Paradoxical embolism is a recognized complication of foramen ovale (PFO) and case reports have linked it to AIS or AMI in young patients[13]
Hypotensive stroke	It is recognized that syncope or presyncope may rarely potentiate stroke, as global hypoperfusion can induce tissue infarction but such events are generally reported to occur in the presence of severe large artery stenosis or during cardiac arrest[14,15] Hypotension-induced infarction preferentially occurs in flow-vulnerable borderzone regions of the brain. Laminar flow through a vessel is proportional to the fourth power of the radius and is inversely proportional to eight times its length, so hypotension preferentially affects longer, distant, narrow vessels that supply the borderzone region[16]
Aortic dissection	AMI and AIS are serious and imminently life-threatening complications of an extensive type I aortic dissection. Rarely in the literature have there been reported cases of concurrent AMI and AIS[17]
Insular stroke	Left insular stroke is associated with an increased risk of adverse cardiac outcome and decreased cardiac wall motion compared to stroke in other locations. After stroke, 10% of patients have adverse cardiac outcomes. Left insular damage may contribute to this by impairing sympathovagal balance associated with cardiac structural damage and arrhythmias[18] The insular cortex damage has been associated with arrhythmia, blood pressure variation disruption and myocardial injury[19] It has been suggested that lesions in the insula may result in abnormal electrocardiographic findings and increase the risk of sudden death. Right insular lesions were related to atrial fibrillation and atrioventricular block, also, compared with left or no insular lesions, increased the odds of death within three months (OR 6.2, 95% CI 1.5 to 25.2) independent of stroke severity, lesions volume, and age[20] Neuroanatomical basis of stroke-related myocardial injury is not totally understood, It is known that cardiac sympathetic overactivity from an insular cortex lesion can provoke diffuse myocardial damage, «myocytolysis», which leads to cardiac enzyme elevation[21,22]
Hematologic disorders and vasculitis	There are cases of hematological disorders (sickle cell anemia, antiphospholipid syndrome, protein C and S deficiency, mutation V Leiden) or cases of vasculitis (Takayasu arteritis, Kawasaki syndrome) that have reported simultaneous events of AIS and AMI[23]

Table 2: The varying rt-PA dose, duration, and method of administration and time frame for initiating therapy in case of AIS, STEMI, and PE.

	Dosage and duration of rt-PA	Time frame for administration
AIS	0.9 mg / kg (maximum dose 90mg), initiate with bolus 10% of the total dose and then infuse the rest in 60 minutes I.V.	Within 3 hours of symptoms onset[a]
STEMI	100 mg, initiate with 15 mg intravenous bolus, followed by 50 mg in infusion in 30 minutes, finally 35 mg in infusion in the following 60 minutes[b]	Up to 12 hours
PE	100 mg in infusion for 2 hours, with 10 mg given as a bolus	Longer duration[c]

a) This period can be extended to 4.5 hours unless any of the following exclusion criteria are present: > 80 years, taking oral anticoagulants regardless of the international normalized ratio, National Institute of Health Stroke Scale (NIHSS) > 25, and patients with a prior history of stroke and diabetes.
b) For patients weighing 67 kg or less, 15 mg are administered in bolus, followed by 0.75 mg / kg infusion in 30 minutes without exceeding 50 mg, and subsequent 0.50 mg/kg for the next 60 minutes without exceeding 35 mg.
c) Some studies demonstrated the thrombolytic therapy remains to be effective up to two weeks after primary embolization.

due to the fact that studies have shown that I.V. rt-PA as the definitive treatment of CCI is not possible because of the different dose of both vascular territories. Alteplase is administered at higher dose for AMI than AIS. (For example, for a 70 kg patient, the dose of AMI is 100 mg and that of acute ischemic stroke is 63 mg). An increased risk of hemorrhagic conversion of AIS when thrombolytic are administered at higher doses and administration of lower than recommended dose of a thrombolytic for AMI may be considered under-dosing, in any case, the percutaneous coronary intervention with stent is the first line therapy for AMI.[4,30-33]

According to the scientific statement from the American Heart Association/American Stroke Association (AHA/ASA), another reasonable approach to the acute management of CCI is a combined treatment of both vascular territories with administration of IV rt-PA at 0.9 mg/kg (maximum of 90 mg) infused for 60 minutes, with 10% of the total dose administered as an initial intravenous bolus for 1 min, followed by percutaneous coronary angioplasty (PCA) and stenting is reasonable (class IIa, level of evidence C), based on the fact that pretreatment with IV rt-PA does not decrease the coronary benefit of PCA and stenting.[2,34]

The ideal management of CCI is a treatment strategy that benefits both vascular territories, in that way when non hyperacute CCI is present (> 4.5 hours) and it is not allowed intravenous thrombolysis for AIS, mechanical thrombectomy, a procedure that is not available in most hospitals, could theoretically be combined with PCA.[35]

Advantages of this approach include the visualization of both coronary and cerebral artery occlusions, which confirms a definite CCI diagnosis, and the effectiveness in treating coronary and cerebral artery occlusion which carries significantly lower mortality than intravenous thrombolysis alone.[4]

To date, not a single CCI case has been reported in Mexico that has been treated in such way. Hence the benefits and complications of a double interventionist therapy are still unknown. In this article we made an approach with intra-arterial thrombolysis plus cerebral thrombectomy followed by percutaneous coronary angioplasty and stenting. This treatment shows promising results for the non-hyperacute synchronous CCI.

Few cases of the CCI have been reported worldwide, and each was treated in a particular way, thus finding a different clinical evolution in each case *(Table 3)*.

OBJECTIVES

The present review aims at examining the pathophysiology, etiology, and the current treatment options of CCI, in addition we suggest an innovative therapy by double percutaneous approach. We also exposing a successful case with this therapy which is the first case in Mexico described with this favourable results.

CLINICAL CASE

A 46-years-old male, active smoker, obese with a BMI of 32 kg/m^2 and diabetic with 10 years of evolution, currently under treatment with metformin and insulin.

The clinical case starts with left hemiparesis, deviation of the lips to the right, dysarthria, dyslalia, impossibility to walk, disorientation and nausea. He is taken into the hospital under the presumed diagnosis of AIS. He arrives to emergency department five hours later. The following vital signs are measured: blood pressure (140/90 mmHg), pulse (110 beats per minute), respiratory rate (19 breaths per minute), oxygen saturation (93%), body temperature (37.3 ºC), clinically disoriented, left-sided facial hemiparesis, positive left Babinski sign, no data regarding meningeal irritation. He referred precordial oppressive pain in a scale of EVA 5/10, diaphoresis, not spread elsewhere. General laboratories are carried out which show not significant results.

Weighing the possibility of AIS a cranial CT scan is immediately done. The results showed a hypodense area in the right temporoparietal region, which suggested AIS of MRCA. After this, an axial magnetic resonance (MRI) was done. We saw a hyperintensity in the territory of MRCA *(Figure 1)*, what guided us to the diagnosis of AIS of the MRCA in acute state. There was an evident mismatch flair-diffusion (DWI) *(Figure 2)*. The patent was ranked with NIHSS of 15 points, which catalogues him as an optimum candidate for a mechanical thrombectomy therapy. On a later stage, following the diagnosis protocol and because he referred precordial pain, an electrocardiogram is carried out, showing V1-V4 S-T elevation *(Figure 3)*. Further blood tests are carried out to get the cardiac enzymes, which were six times above the normal upper limit. These results made possible the diagnosis of anteroseptal STEMI. A basal transthoracic echocardiogram

Table 3: CCI Results and cases reported worldwide.

Case	Sex/age	Cardiac Treatment	Neurological treatment	Result
Park 2008	F - 78 y/o	PCA	Medical treatment	Partial improvement
Park 2008	M - 60 y/o	PCA	urokinase	Partial improvement
Natarajan 2016	F - 60 y/o	PCA	No reported	Coma
Grogono 2012	F - 39 y/o	PCA-PFO	No reported	No reported
Soan 1992	M - 37 y/o	Antiplatelet therapy	No reported	Hemiparesis
Wee 2015	M - 49 y/o	PCA	Clopidogrel 300 mg	mRS 2
Castillo 2016	F - 61 y/o	PCA	No reported	No reported
Gonzalez 2014	F - 66 y/o	rt-PA + PCA	rt-PA	NIHSS 5
Kim 2013	M - 58 y/o	Clopidogrel + PCA	ASA[1]	No reported
Hosoya 2017	M - 50 y/o	Antiplatelet therapy	None	Hemiparesis
Akyuz 2012	M - 43 y/o	PCA + rt-PA	No reported	Hemianopia
Maciel 2015	M - 44 y/o	Medical treatment	rt-PA	mRS 2 (NIHSS 9)
Omar 2010	M - 48 y/o	Medical treatment	Medical Treatment	Death
Cerón, Plata 2018	**M - 46 y/o**	**PCA + stent**	**Intra-arterial thrombolysis + cerebral thrombectomy**	**Total Improvement**

Acetylsalicylic acid[1].

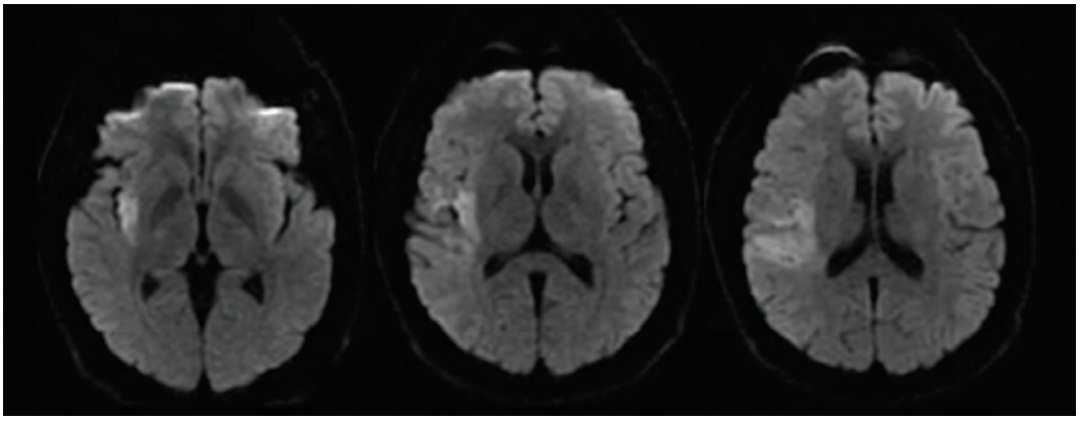

Figure 1:

MRI DWI sequence, where the right insular lesion is evident.

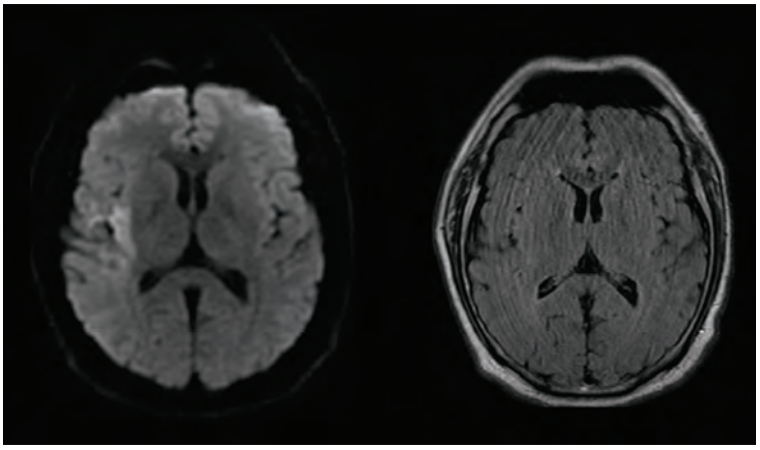

Figure 2: MRI DWI sequence where the right insular lesion is evident, and MRI T2 FLAIR sequence shows no evident lesion (mismatch FLAIR-DIFUSION). This suggests that the ischemic lesion had less than 6 hours, evolution.

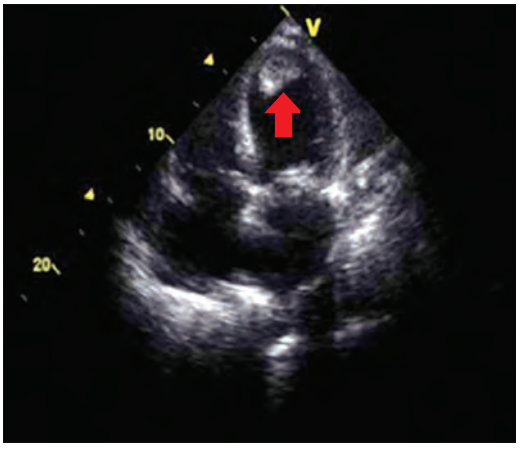

Figure 4: Transthoracic echocardiogram apical four-chamber view demonstrating a large apical thrombus (arrow).

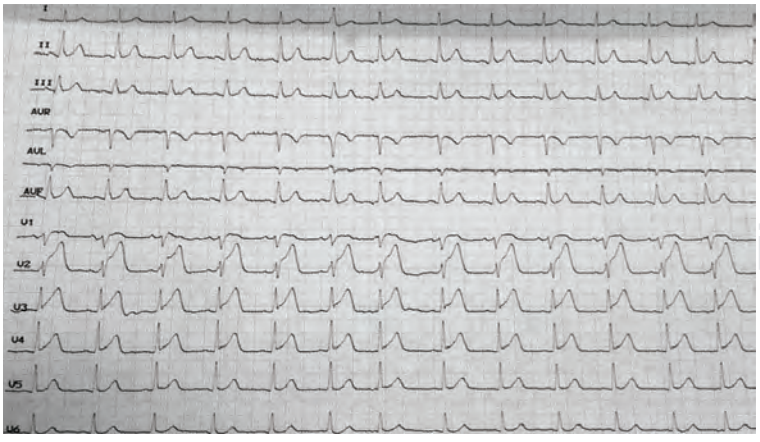

Figure 3: V1-V4 S-T elevation showed in ECG.

showed ejection fraction of 60%, left ventricular hypokinesia and the presence of left apical thrombus *(Figure 4)*. Later on, the patient was subjected to a coronariography, which showed a subocclusion of the proximal LAD.

Non-hyperacute CCI was diagnosed and a double interventionist approach was carried out. A cerebral angiography was performed, showing occlusion of the MRCA in the M2 segment. We decided to start with intra-arterial thrombolysis with rt-PA 5 mg in bolus, followed by mechanic thrombectomy with which proves to be successful *(Figure 5)*. On a cardiac level, coronariography with angioplasty was performed by placing a drug-eluting stent in the proximal segment of the LAD reaching flow TIMI-3 *(Figure 6)*.

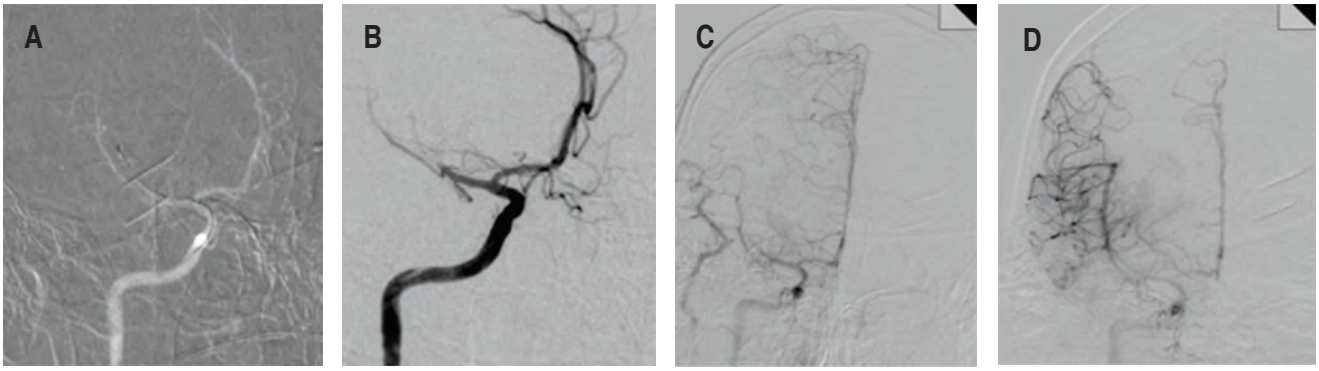

Figure 5: Cerebral angiography which shows the occlusion of the MRCA M2 segment **(A** y **B)**, reperfusion sequence **(C** y **D)**.

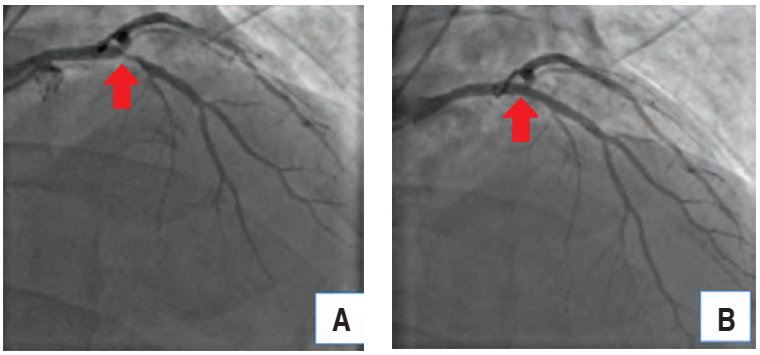

Figure 6: Coronariography shows occlusion of the proximal segment of LAD **(A)**, with reperfusion sequence **(B)**.

Both procedures were carried out without any eventualities. Medication with antiplatelet, statins, ACEIs and warfarin was started after both procedures. The patient was discharged on the third day showing an electrocardiogram without ischemic changes and a mRS of 2.

DISCUSSION

This article talks about a 46-years-old male, which is below the age mean of registered cases. Nonetheless, the patient has prothrombotic risk factors such as: smoking, obesity and diabetes, making him vulnerable to vascular damage at an early age.

The etiology in this case is due to the LAD occlusion and dysfunction of the left ventricle, which caused left ventricular hypokinesia. This added to the prothrombotic state gave place to the formation of left ventricular thrombus that could were later embolized.

Even though the diagnosis of the CCI is normally incidental or diagnosed by autopsy, this time it was hinted by the clinic profile of the patient. He showed chest pain and left hemiparesis, and the occlusion of both vascular territories was confirmed immediately by angiography.

Patients who cannot refer the exact time of the start of their symptoms, a good indicative of the elapsed time is the MRI. If the MRI shows a mismatch DWI-FLAIR, a time lapse of less than 4.5-6 hours can be inferred with high specificity. If the FLAIR sequence shows evidence of lesion, then a time-lapse of more than 6 hours can be inferred. In fact, to some neurointerventionists the occurrence of a mismatch DWI-FLAIR is enough to start thrombolytic therapy when the patient cannot clearly state when started presenting symptoms.[25-28]

The regular treatment offered to these patients is focused on angioplasty and the use of stents, at a cardiac level, leaving AIS in observation, leading to severe neurological deficit.

The treatment offered to our patient is unique because very few patients come in the therapeutic window necessary for an interventionist approach. Furthermore, not all hospitals have the right facilities to take such approach. PCA and colocation of drug-eluting stent in LAD, plus intra-arterial thrombolysis with rt-PA associated with mechanic thrombectomy of MRCA M2 segment was performed.

The majority of the clinical essays about endovascular therapy in AIS talk about the administration of IV rt-PA alongside the use

of endovascular therapy. Nonetheless, the analysis of the subgroups of some clinical essays showed that patients who received thrombectomy therapy without IV rt-PA (due to contraindication), had functional independence and a more rapid rate of recovery than patients who were administered IV rt-PA with endovascular therapy.[36,37]

Because of this and because our patient was out of the therapeutic window, we decided not to apply intravenous thrombolytic therapy, and to administer intra-arterial thrombolytic therapy, as multiple studies recommend.

It is known that intra-arterial thrombolysis may provide multiple benefits in acute stroke treatment, including extending the treatment therapeutic window, tailored thrombolytic dosage and delivery, salvage therapy for IV rt-PA non responders, and combined use with other endovascular techniques, even in several series, mechanical approach in conjunction with intra-arterial thrombolysis has been shown to achieve higher rates of stroke recanalization and excellent functional outcome can be achieved.[38,39]

About the dosage, intra-arterial rt-PA is commonly used during mechanical thrombectomy for acute ischemic stroke in patients with large-vessel occlusion. In MR RESCUE TRIAL, a maximum of 14 mg of intra-arterial rt-PA was allowed, the mean dose given was 5.1 mg (2 mg-12 mg). MR CLEAN TRIAL allowed for intra-arterial thrombolytic use, with maximum rt-PA doses of 30 mg. Some studies administer 5 mg at 3 time points during mechanic thrombectomy: (1) upon catheterization of the cervical internal carotid artery, (2) at stentriever clot engagement, and (3) postrecanalization. The theory behind this dosing strategy is that the initial dose helps to further soften the proximal end of the thrombus for crossing with the microwire and microcatheter, the second dose is to assist the stent in absorbing into the clot before retrieval, and the third is to help dissolve microemboli that may occur despite aspiration.[40]

After therapy the patient was discharged showing an electrocardiogram without ischemic changes and a mRS of 2. The patient is asked to come for an appointment fifteen and thirty days after his discharge. A new transthoracic echocardiogram is done showing ejection fraction of 65% without valvular disease or intracavitary thrombus, no pulmonary hypertension, no hypokinetic areas either. The patient shows a favorable neurological evolution, reclassifying at day 15 with mRS of 1, and 0 at day 30 after his discharge. The evolution of our patient with the therapy used was optimal, without neurological deficit or cardiohemodynamic compromise.

CONCLUSION

We recommend that every single patient who arrives under presumptive diagnostics of AIS must be protocolized for probable concomitant cardiac compromise with an electrocardiogram and cardiac enzymes. If positive, the next step will be to know how long ago the symptoms started: if < 4.5 hours, the approach will be the administration of IV rt-PA followed by percutaneous coronary angioplasty and stenting. If > de 4.5 hours (non-hyperacute state) we suggest an approach with cerebral thrombectomy alongside coronary angioplasty and stenting. The advantages of addressing non-hyperacute CCI in this way include the visualization of coronary and cerebral arterial occlusions that confirm the diagnosis; and the possibility to start treatment by endovascular approach at the same time. We suggest intra-arterial therapy with rt-PA when patients are no candidates for IV thrombolytic therapy. Further studies are needed to determine the benefits and complications of this approach.

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REFERENCES

1. Jong Kyu P, Sang-Hak L, Seonghoon C, Jae-Hun J, Namho L. Two patients with acute myocardial infarction presenting with simultaneous acute ischemic stroke. Korean J Med. 2008; 74 (6): 672-625.
2. Akinseye OA, Shahreyar M, Heckle MR, Khouzam RN. Simultaneous acute cardio-cerebral infarction: is there a consensus for management? Ann Transl Med. 2018; 6 (1): 7.
3. Omar HR, Fathy A, Rashad R, Helal E. Concomitant acute right ventricular infarction and ischemic

cerebrovascular stroke; possible explanations. Int Arch Med. 2010; 3: 25.
4. Yeo LLL, Andersson T, Yee KW, Tan BYQ, Paliwal P, Gopinathan A et al. Synchronous cardiocerebral infarction in the era of endovascular therapy: which to treat first? J Thromb Thrombolysis. 2017; 44 (1): 104-111.
5. Kijpaisalratana N, Chutinet A, Suwanwela NC. Hyperacute simultaneous cardiocerebral infarction: rescuing the brain or the heart first? Front Neurol. 2017; 8: 664.
6. Budaj A, Flasinska K, Gore JM, Anderson FA, Dabbous OH, Spencer FA et al. Magnitude of and risk factors for in-hospital and postdischarge stroke in patients with acute coronary syndromes. Circulation. 2005; 111 (24): 3242-3247.
7. Gattringer T, Niederkorn K, Seyfang L, Seifert-Held T, Simmet N, Ferrari J et al. Myocardial infarction as a complication in acute stroke: results from the austrian stroke unit registry. Cerebrovasc Dis. 2014; 37 (2): 147-152.
8. Mochmann H-C, Scheitz JF, Petzold GC, Haeusler KG, Audebert HJ, Laufs U et al. Coronary angiographic findings in acute ischemic stroke patients with elevated cardiac troponin. Circulation. 2016; 133 (13): 1264-1271.
9. Gianstefani S, Douiri A, Delithanasis I, Rogers T, Sen A, Kalra S et al. Incidence and predictors of early left ventricular thrombus after ST-elevation myocardial infarction in the contemporary era of primary percutaneous coronary intervention. Am J Cardiol. 2014; 113 (7): 1111-1116.
10. Delewi R, Zijlstra F, Piek JJ. Left ventricular thrombus formation after acute myocardial infarction. Heart. 2012; 98 (23): 1743-1749.
11. Vaitkus PT, Barnathan E. Embolic potential, prevention and management of mural thrombus complicating anterior myocardial infarction: a meta-analysis. 1993; 1004-1009.
12. Tokuda K, Shindo S, Yamada K, Shirakawa M, Uchida K, Horimatsu T et al. Acute embolic cerebral infarction and coronary artery embolism in a patient with atrial fibrillation caused by similar thrombi. J Stroke Cerebrovasc Dis. 2016; 25 (7): 1797-1799.
13. Grogono J, Fitzsimmons S, Shah B, Rakhit D, Gray H. Simultaneous myocardial infarction and ischaemic stroke secondary to paradoxical emboli through a patent foramen ovale. 2012; 391-392.
14. Bladin CF, Chambers BR. Frequency and pathogenesis of hemodynamic stroke. 1994. pp. 2179-2182.
15. Dobkin B. Orthostatic hypotension as a risk factor for symptomatic occlusive cerebrovascular disease. 1989. pp. 30-34.
16. Ryan D, Kenny R, Christensen S, Meaney J, Fagan A, Harbison J. Ischaemic stroke or TIA in older subjects associated with impaired dynamic blood pressure control in the absence of severe large artery stenosis. 2015.
17. Nguyen TL, Rajaratnam R. Dissecting out the cause: a case of concurrent acute myocardial infarction and stroke. 2011;
18. Laowattana S, Zeger SL, Lima JAC, Goodman SN, Wittstein IS, Oppenheimer SM. Left insular stroke is associated with adverse cardiac outcome. Neurology. 2006; 66 (4): 477-4783.
19. Nagai M, Hoshide S, Kario K. The insular cortex and cardiovascular system: a new insight into the brain-heart axis. J Am Soc Hypertens. 2010; 4 (4): 174-182.
20. Christensen H, Boysen G, Christensen AF, Johannesen HH. Insular lesions, ECG abnormalities, and outcome in acute stroke. J Neurol Neurosurg Psychiatry. 2005; 76 (2): 269-271.
21. Ay H, Koroshetz WJ, Benner T, Vangel MG, Melinosky C, Arsava EM et al. Neuroanatomic correlates of stroke-related myocardial injury. Neurology. 2006; 66 (9): 1325-1329.
22. Cheshire WP, Saper CB. The insular cortex and cardiac response to stroke. Neurology. 2006; 66 (9): 1296-1297.
23. Hosoya H, Levine JJ, Henry DH, Goldberg S. Double the trouble: acute coronary syndrome and ischemic stroke in polycythemia vera. The Am J Med. 2017; 130 (6): e237-e240.
24. Jauch EC, Saver JL, Adams HP, Bruno A, Connors JJ, Demaerschalk BM et al. Guidelines for the early management of patients with acute ischemic stroke. Stroke. 2013; 44 (3): 870-947.
25. De Silva DA, Manzano JJF, Chang HM, Wong MC. Reconsidering recent myocardial infarction as a contraindication for IV stroke thrombolysis. Neurology. 2011; 76 (21): 1838-1840.
26. Bueno H, Martínez-Sellés M, Pérez-David E, López-Palop R. Effect of thrombolytic therapy on the risk of cardiac rupture and mortality in older patients with first acute myocardial infarction. 2005; 1705-1711.
27. Chang RY, Tsai HL, Hsiao PG, Tan CW, Lee CP, Chu IT et al. Comparison of the risk of left ventricular free wall rupture in Taiwanese patients with ST-elevation acute myocardial infarction undergoing different reperfusion strategies: a medical record review study. 2016; e5308.
28. Patel M, J Meine T, Lindblad L, Griffin J, Granger C, Becker RC et al. Cardiac tamponade in the fibrinolytic era: analysis of > 100,000 patients with ST-segment elevation myocardial infarction. 2006; 316-322.
29. Omar H, Mangar D, Camporesi E. Simultaneous thrombosis of 2 vascular territories: is thrombolytic therapy a better option? 2013.
30. Álvarez-Sabín J, Maisterra O, Santamarina E, Kase CS. Factors influencing haemorrhagic transformation in ischaemic stroke. Lancet Neurol. 2013; 12 (7): 689-705.
31. Brott TG, Haley EC, Levy D, Barsan W, Broderick J, Sheppard GL et al. Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. 1992; 632-640.
32. Messé SR, Tanne D, Demchuk A, Cucchiara B, Levine SR, Kasner S. Dosing errors may impact the risk of rt-PA for stroke: the multicenter rt-PA acute stroke survey. 2004; 35-40.
33. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018; 49 (3): e46-e99.
34. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC et al. Scientific

rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke. Stroke. 2016; 47 (2): 581-641.
35. Maciel R, Palma R, Sousa P, Ferreira F, Nzwalo H. Acute stroke with concomitant acute myocardial infarction: will you thrombolyse? 2015.
36. Goyal M, Demchuk A, Menon B, Eesa M, Rempel J, Thornton J et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. 2015.
37. Campbell B, Mitchell P, Kleinig T, Dewey HM, Churilov L, Yassi N et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. 2015.
38. Noser EA, Shaltoni HM, Hall CE, Alexandrov AV, Garami Z, Cacayorin ED et al. Aggressive mechanical clot disruption: a safe adjunct to thrombolytic therapy in acute stroke? Stroke. 2005; 36 (2): 292-296.
39. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015; 372 (1): 11-20.
40. Heiferman DM, Li DD, Pecoraro NC, Smolenski AM, Tsimpas A, Ashley WW, Jr. Intra-arterial alteplase thrombolysis during mechanical thrombectomy for acute ischemic stroke. J Stroke Cerebrovasc Dis. 2017; 26 (12): 3004-3008.

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Clinical case

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Sinus of Valsalva aneurysm that fistulizes into the right atrium

Aneurisma del seno de Valsalva que fistuliza en la aurícula derecha

María Fernanda Rabascall Cobos,* Ernesto Peñaherrera**

Keywords:
Valsalva sinus aneurysm, cardiac insufficiency, cardiovascular diagnostic techniques, echocardiography.

Palabras clave:
Aneurisma del seno de Valsalva, insuficiencia cardiaca, técnicas de diagnóstico cardiovascular, ecocardiografía.

ABSTRACT

The Valsalva sinus aneurysm is a rare entity in the general population, with an incidence between 0.14 and 3.5% in open-heart surgeries, with a wide clinical spectrum and both electrical and mechanical complications. We present the case of a patient with an aneurysm of the right sinus of Valsalva that fistulized to the right atrium and was complicated with heart failure. The echocardiographic images that were useful to establish the diagnosis and the therapeutic measures are shown, as well as a review of the topic.

RESUMEN

El aneurisma del seno de Valsalva es una entidad rara en la población general, con una incidencia entre 0.14 y 3.5% en cirugías de corazón abierto, con un amplio espectro clínico y complicaciones tanto eléctricas como mecánicas. Se presenta el caso de un paciente con aneurisma del seno de Vasalva derecho fistulizado hacia aurícula derecha complicado con insuficiencia cardiaca. Se muestran las imágenes ecocardiográficas que fueron útiles para establecer el diagnóstico y las medidas terapéuticas, además de una revisión del tema.

INTRODUCTION

The Valsalva aneurysm was described in 1839[1,2] all presented in Valsalva sinuses of the aortic valve and not in the pulmonary artery. It is a rare entity, with an incidence between 0.14 and 3.5% in open heart surgeries.[1]

They are dilatations of the sinus due to a weakness of the middle layer of the aortic wall.[3] This fragility of the aortic wall is explained due to a defective union of the exit tract, valvular ring and anterior wall of the aorta.[4] They may be congenital or acquired. Those of acquired type are due to degenerative, infectious, traumatic causes, connective tissue diseases such as Marfan syndrome or Ehlers-Danlos syndrome, although in these pathologies rupture is extremely rare.[5] These aneurysms progressively dilate until they rupture towards the 4 cavities of the heart,[6] less frequently they break into the pulmonary artery, pericardium, vena cava, pleural cavity. They are associated with other congenital anomalies such as the interatrial or interventricular septum defect, bicuspid aortic valve, aortic insufficiency, coarctation of the aorta, patent ductus arteriosus, quadricuspid pulmonary valve, pulmonary stenosis, anomalies of the origin of the coronary arteries.

The factors that contribute to the formation and rupture of the Valsalva sinus aneurysms are: low implantation of the valvular annulus, defective development of the conal septum or of the endocardial bearings of the aortic and pulmonary valves and the high pressure of the aorta.

Clinical spectrum is very wide. We can find asymptomatic patients in the case that the aneurysm is intact and the Valsalva sinus aneurysm is an incidental diagnosis, or symptomatic patients with mechanical complications such as fistulized Valsalva sinus aneurysm, heart failure, infectious endocarditis, open rupture to pericardium, acute myocardial infarction and electrical complications such as complete atrioventricular block, these last three causes can lead to sudden death.[1,2]

We report a case of a patient with a right sinus of Valsalva aneurysm that fistulized to

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the right atrium with surgical repair being the treatment of choice.

The clinical history of our patient that denies data such as cardiac surgery, fever or sudden episode of chest pain inclines us to think that it is a problem acquired with a gradual and progressive perforation with surgical repair being the treatment of choice.

CLINICAL CASE

We present the case of a 44-year-old male patient, resident in Manta-Ecuador, tobacco user, without past cardiovascular diseases. Past medical history: hepatic cirrhosis diagnosed 8 years ago without treatment and non-dialytic chronic renal failure (6 months). He entered our institution due to a history of 6 months characterized by dyspnea of medium to minimal efforts, ascites, oedema in the lower extremities and palpitations. He had symptomatic right heart failure due to dyspnea, ascites and oedema in the lower extremities. Blood pressure at admission was 90/60 mmHg, tachyarrhythmic, with a heart rate of 100 beats per minute, and a respiratory rate of 24 breaths per minute.

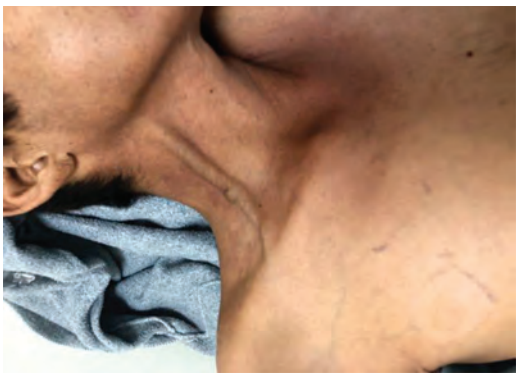

Figure 1: Jugular Ingurgitation III/III.

Physical examination revealed elevated jugular venous pressure, jugular vein III/III *(Figure 1)*, bilateral rales, continuous pansystolic murmur in the base and mesocardium, painful hepatomegaly, hepatojugular reflux, ascites, and oedema in the lower extremities 5/6. A chest X-ray was performed that showed an increase in cardiac silhouette at the expense of right cavities. Hemogram, anemia, impaired renal, hepatic and ionogram function, natriuretic peptide and elevated C-reactive protein. An electrocardiogram was performed showing atrial fibrillation of moderate ventricular response, hypertrophy of the right ventricle with disorders of ventricular repolarization *(Figure 2)*. A transthoracic echocardiogram showed a left ventricle with increased ventricular volumes, with moderate systolic dysfunction, a dilated and hypokinetic right ventricle with a TAPSE of 12 mm and a tissue S wave of 4 cm, flattening of the interventricular septum (SIV), overload to right ventricle due to left-to-right shunt with a pulmonary artery systolic pressure

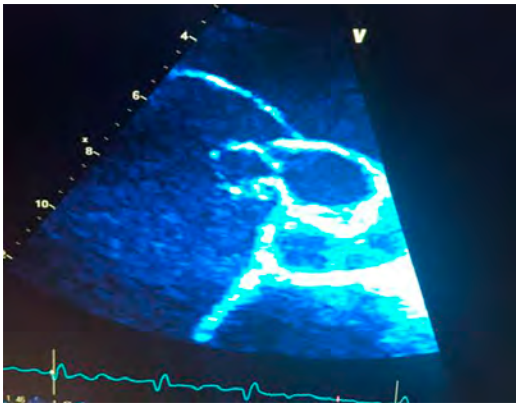

Figure 3: Color Doppler echocardiogram: Short axis: Valsalva sinus aneurysm that communicates with the right atrium.

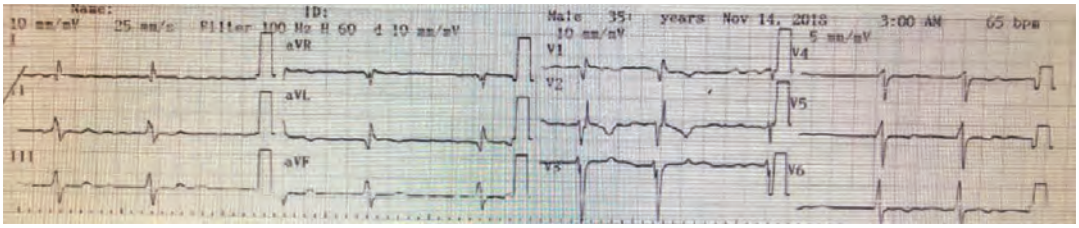

Figure 2: EKG: Atrial fibrillation of moderate ventricular response (FAMRV).

(PSAP) of 48mmHg, acceleration time (TAC) 65 m. In the short axis at the level of the great vessels an annular, very well defined image was observed floating inside the right atrium (AD) *(Figures 3 and 4)*. With the transesophageal echocardiogram a right sinus of Valsalva aneurysm that fistulized to the right atrium (Sakakibara type IIIa classification) was observed. With color Doppler and continuous Doppler it was observed a continuous, turbulent, high-velocity flow between the fistulized aneurysm and right atrium *(Figure 5)* with a gradient of 60 mmHg. This flow begins in the systole and extends until the diastole, differentiating itself from the tricuspid regurgitation flow. Left and right cardiac catheterization was performed observing normal coronary arteries and without significant lesions, passage of contrast from the aorta to the right atrium through what looks like a fistula between the right Vasalva sinus and the right atrium *(Figure 6)*, with a broad trajectory of about 6-8 mm, severely dilated right atrium, increased right cavity pressures, right atrial pressure (DBP): 25 mmHg, right ventricular pressure (PVD): 49/0-6, moderate pulmonary hypertension PSAP 52/30, PAMP 40, pulmonary vascular resistance (PVR): 82 dynes, systemic vascular resistance (SVR): 648 dynes, pulmonary vascular resistances are slightly increased, with a cardiac output (CO) of 6.7 L/min/m^2 and a cardiac index (CI): 4.7 L/min/m^2, increased by the great hyperflow caused by the left-right fistula.

Treatment

Pharmacological treatment was initiated with diuretics such as intravenous furosemide and

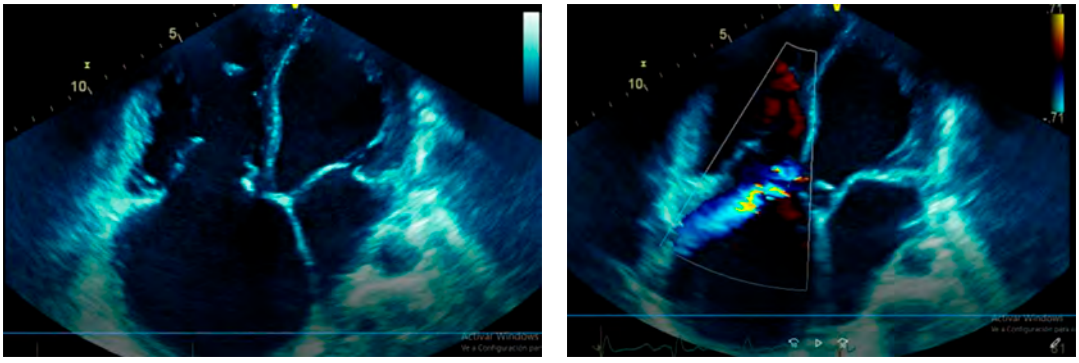

Figure 4: Color Doppler echocardiogram: Apical 4 chambers: Dilation of right cavities. With color Doppler, a communication is observed between the ruptured right Valsalva sinus aneurysm and the right atrium.

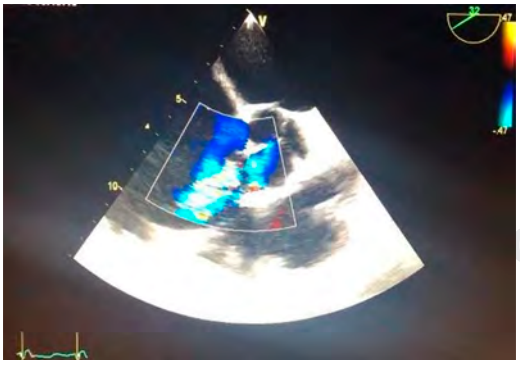

Figure 5: Ecotransesophageal: Short axis. With color Doppler, a communication is observed between the ruptured right Valsalva sinus aneurysm and the right atrium.

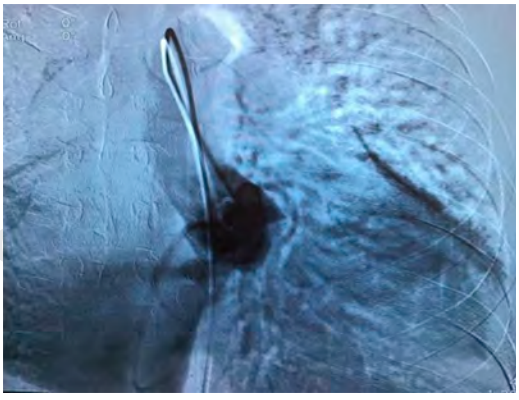

Figure 6: Catheter: Contrast step from the sinus of Vasalva right fistulized towards the right atrium.

water restriction to achieve a negative balance and inotropic drugs such as dobutamine to maintain anterograde perfusion. This case is presented to the medical-surgical staff and they decided to perform surgery to repair Vasalva's right sinus. The patient underwent surgery, during the procedure right aortoatrial fistula was observed from the right aortic sinus infra ostial coronary. A fistulamarsupialization was performed with right atriotomy, fistula closure, atrioraphy, aortorrhaphy, electrical and pharmacological cardioversion due to ventricular fibrillation and transient pacemaker due to extreme bradycardia secondary to the pharmacological effect of amiodarone. A transthoracic control echocardiogram was performed, which revealed the absence of residual or new aortoatrial fistula. The patient responds favorably being discharged and control by external consultation.

DISCUSSION

Vasalva sinus aneurysms can develop in any of the 3 sinuses, being the most frequent in the right one (67.5-93.4%), then the non-coronary (25-29%) and the last place the left (1-8%).[7] Aneurysms of the right sinus rupture more frequently to the right ventricle (60%), right atrium (29%), left atrium (6%), left ventricle (4%) or pericardium (1%).[8]

It is known to be five times more frequent in Asian countries than in Western countries.[9] The male gender is the most affected with 65% to 80% of cases and a male / female ratio of 4: 1.[10]

According to the study group of De Bakey et al., the anomalies of the sinus of Valsalva can be classified into three groups:[11]

1. Aneurysm of the sinus.
2. Aneurysm with fistula.
3. Fistula.

In our case, the presence of an aneurysm with a fistula was documented to the right atrium, belonging to group 2.

The diagnosis can be made by color-Doppler echocardiography and transesophageal echocardiogram. Those studies give sufficient information to make the diagnosis.[12] It is also necessary to perform the catheterization because they have other cardiac anomalies. In our case, the transthoracic echocardiogram allowed us to observe the rupture of the sinus of Valsalva in the first instance, so it was necessary to complete the approach with a transesophageal echocardiogram and aortogram.

If there is a rupture, the supraventricular arrhythmias can be found on the electrocardiogram, especially atrial fibrillation, electrical axis displaced to the right, right ventricular hypertrophy. When aneurysm ocurs without rupture, the electrocardiogram is usually normal unless the atrioventricular node or any of its branches is compressed, and we can find complete atrioventricular block or other atrioventricular conduction abnormalities.[13] In the case of our patient, we found by electrocardiogram, atrial fibrillation rhythm, right ventricular hypertrophy data and ventricular repolarization disorders.

The natural evolution of the aneurysm may be rupture to a cavity, usually right, causing a left-to-right shunt. The physiopathological and clinical consequences will depend on how fast the rupture occurs, the magnitude of the shunt and the receiving cavity. When the rupture occurs abruptly and the shunt is important, it generates rapid onset of pulmonary congestion, severe and progressive heart failure,[12] of poor prognosis if left to its evolution. If the rupture is slow and the shunt is small, it can go unnoticed for a long time, with bacterial endocarditis being the complication of greatest risk in this phase. When a ruptured or intact aneurysm penetrates the base of the interventricular septum, a complete heart block occurs and causes syncope or death.

Our patient presented signs of hemodynamic overload of the right cavities from a clinical, electrocardiographic and echocardiographic point of view.

In 1962, Sakakibara and Konno established the classification of the Valsalva aneurysms, which is still valid. They classified them into 4 types according to the coronary sinus affected and the area where they fistulized, with 3 subdivisions being type III *(Table 1)*.[13]

The case corresponds to a Vasalva type IIIa aneurysm of this classification

Table 1: Classification of sinus aneurysms of Valsalva.[13]

Type I: Connects the right SV and the RV exit tract below the pulmonary valve
Type II: Connects the right SV and RV in the supraventricular crista
Type III a: Connects the right SV and the AD
Type III v: Connects the posterior area of the right SV and the RV
Type III a + v: Connect the right SV and both, AD and VD
Type IV: Connects the non-coronary SV and the right atrium

SV = Sinus of Valsalva, AD = Right atrium, VD = Right ventricle.

The absolute indications for surgery in unruptured aneurysms are obstruction of the outflow of the right ventricle, infection, arrhythmias or obstruction of a coronary artery.[14] The closure of the fistula is recommended even in asymptomatic patient, due to relatively few complications related to the procedure and the risk of complications such as heart failure, bacterial endocarditis, pulmonary vascular disease, formation of other aneurysms and spontaneous rupture, are greater if such surgery is not performed.[14]

In addition, repair surgery entails immediate results and reduces the risk of the aforementioned complications, improving the life expectative of patients.[15]

Open surgery is the most used technique, although there are successful reports of percutaneous closure.[16] Surgical correction is usually simple, and it can be done almost always through an aortic approach, with a mortality lower than 1% and with a survival at 5 and 10 years of 97 and 90%, respectively.[15] It has been suggested that perioperative mortality increases from 4 to 5 times in cases of infection or endocarditis.[10,17] Special mention is made of patients with large fistulas in whom the function of the aortic valve has been compromised or fistulas that are located near the coronary ostium which the procedure is more difficult, since coronary or valvular surgery techniques should be associated.

Recurrence of a fistula, after corrective surgery, is rare, reporting around 3% according to the series of Van JA and collaborators.[18]

CONCLUSION

The present case allows us to observe the clinical evolution and the importance of an early diagnosis in a patient with aneurysm of the right sinus that is perforated to the right atrium presenting heart failure and intense continuous heart murmur.

The final diagnosis is heart failure due to overload of the right atrium secondary a left to right shunt. The transthoracic and the transesophageal echocardiograms are decisive in the diagnosis. The treatment for Valsalva sinus aneurysms that fistulize to another receiving chamber is surgical correction because it has excellents results and low mortality.

BIBLIOGRAPHY

1. Alva C, Vásquez C. Congenital aneurysm of the sinus of Valsalva. Revisión Rev Mex Cardiol. 2010; 21: 104-110.
2. Serrano EA, Basso GH, Flórez CE, Como JH. surgery of the sinus of Valsalva. Rev Fed Arg Cardiol. 2007; 36: 40-41.
3. Edwards JE, Burchell HB. The pathological anatomy of deficiencies between the aortic root and the heart including aortic sinus aneurysm. Thorax. 1957; 12: 125.
4. Sakakibara S, Konno S. Congenital aneurysm of the sinus of Valsalva. Am J Cardiol. 1963; 12: 100.
5. Guo DW, Cheng TO, Lin ML, GUZQ. Aneurysm of the Sinus of Valsalva: A roentgenology study of 165 Chinese patients. Am Heart J. 1987; 114: 1169-1177.
6. Munk MD, Gatzoulis MA, King DE, Webb GD. Cardiac tamponade and death from intrapericardial of sinus of Valsalva aneurysm. Eur J Cardio Thorac Surg 1999; 15: 100-102.
7. Chu SH, Hung CR, How SS, Chang H, Wang SS, Tsai CH. Ruptured aneurysms of the sinus of Valsalva in Oriental patients. J Thorac Cardiovasc Surg. 1990; 99: 288-298.
8. Galicia-Tornell MM, Marín-Solís B, Mercado-Astorga O, Espinoza-Anguiano S, Martínez-Martínez M, Villalpando- Mendoza E Aneurysm of the Sinus of Valsalva. Case report and literature review. Cirug. 2009; 77: 473-477.
9. Abbott M. Clinical and developmental study of a case with ruptured aneurysm of the right anterior aortic sinus of Valsalva: Contributions to medical and biological research, Vol 2. New York. Hoeber 1919; 899.
10. Kanzaki Y, Terasaki F, Fuji S, Kashiyama T, Kaibe S, Doi Y. A sinus of Valsalva-right atrium fistula without aneurysm formation. Inter Med. 2010; 49: 749-751.
11. Sakakibara S, Konno S. Congenital aneurysm of the sinus of Valsalva. Anatomy and classification. Am Heart J 1962; 3: 405-422.
12. Baur LH, Vliegen HW, Van der Wall EE, Hazckamp M, et al. Imaging of an aneurysm of the sinus of Valsalva with transesophageal echocardiography, contrast angiography and MRI. Intern J Cardiac Imag 2000; 16: 34-41.
13. Gorocito M, Accerboni G, Cabales A y col. Endocarditis infecciosa asociada con ruptura de un aneurisma del seno de Valsalva. Rev Argent Cardiol 2002; 70: 211-213.

14. Takach TJ, Reul GJ, Duncan JM. Sinus of Valsalva aneurysm or fistula: management and outcome. Ann Thorac Surg. 1999; 68 (5): 1573-1577.
15. Ibrahim KS, Waqfi NR, Jarrah MI. Sinus of Valsalva aneurysm with fistula to the right atrium presented as acute heart failure in a young man. Am J Case Rep. 2013; 14: 398-400.
16. Zhao SH, Yan CW, Zhu XY, Li JJ, Xu NX, Jiang SL. Transcatheter occlusion of the ruptured sinus of Valsalva aneurysm with an Amplatzer duct occluder. Int J Cardiol. 2003; 129 (1): 81-85.
17. Ott DA. Aneurysm of the sinus of Valsalva. Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann. 2006; 165-176.
18. Van Son JA, Danielson GK, Schaff HV, Orszulak TA, Edwards WD, Seward JB. Long-term outcome of surgical repair of ruptured sinus of Valsalva aneurysm. Circulation. 1994; 90: 20-29.

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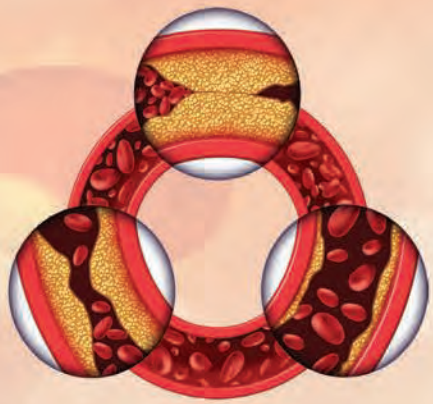

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