A Cardiopatia Isquémica como Exemplo de um Evento Trombótico. Nota Histórica [47]

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RESUMO

A definição da cardiopatia isquémica como entidade clínica de etiologia trombogénica foi estabelecida em 1912 por James Herrick. Na origem desta proposta destacam-se os trabalhos de William Heberden que, em 1772, definiu o quadro clínico da angina *pectoris* e, cerca de um século mais tarde, as observações de Edward Jenner, que evidenciou trombos intracoronários em doentes falecidos com aquela sintomatologia. Fundamentando-se nos anteriores resultados, Jenner e Caleb Parry propuseram que a causa principal da «doença anginosa» tinha origem em alterações das artérias coronárias, sendo a morte súbita naqueles doentes atribuída por Marshall Hall, em 1842, à interrupção da circulação coronária.

A existência de uma causa comum para a angina e o enfarte do miocárdio, de que resultaria a diminuição ou privação do fornecimento de oxigénio relativamente às necessidades de oxigenação do miocárdio, a etiologia aterosclerótica das lesões intracoronárias e a importância da fissura das placas de ateroma na formação súbita de trombos intracoronários, foram etapas sucessivamente ultrapassadas durante o século XX, culminando um percurso de observação meticulosa iniciado muito antes.

Palavras-Chave
Isquemia; Miocárdio; Coronárias; Trombose; História

ABSTRACT

Ischemic Myocardial Disease as an Example of a Thrombotic Event. A Historical Note

The definition of myocardial ischemia as a clinical entity of thrombotic etiology was established in 1912 by James Herrick. His proposal was based on the work of William Heberden, who in 1772 defined the clinical profile of angina pectoris, and the observations of Edward Jenner about a century later on intracoronary thrombosis in patients who had died with such symptoms. On the basis of these results, Jenner and Caleb Parry proposed that the main cause of angina were alterations in the coronary arteries, while Marshall Hall, in 1842, attributed sudden death in these patients to interruption of the coronary circulation.

The discovery of a common cause for angina pectoris and myocardial infarction, inducing a reduction or interruption of oxygen supply to myocardial tissue, the atherosclerotic etiology of intracoronary lesions, and the importance of plaque fissuring in the sudden formation of intracoronary thrombi, were successive milestones in our understanding in the 20th century, the culmination of the process of meticulous observation begun many years before.

Key words
Myocardium; Coronaries; Ischemia; Thrombus; History

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O enfarte de miocárdio foi descrito como entidade clínica, pela primeira vez, pelo clínico norte-americano James B. Herrick, em 1912 [1]. A clareza das suas observações e inteligência de raciocínio fundamentaram grande parte dos conceitos que hoje ainda vigoram sobre a fisiopatologia e clínica da doença isquémica do miocárdio. Adicionalmente, é-lhe devida a utilização sistemática que fez dos electrocardiogramas no diagnóstico e acompanhamento de doentes de enfarte do miocárdio, a qual se tornou uma rotina generalizada algumas décadas mais tarde.

No entender de Herrick, pelo que verificara nos seus doentes e nas descrições clínicas e experimentais de finais do século XIX, aquela situação patológica resultaria da obstrução súbita das artérias coronárias por trombos. Confirmou ainda a gravidade das obstruções do ramo descendente da artéria coronária esquerda como causa frequente de morte súbita; as obstruções ocorridas em outros ramos das artérias coronárias, mesmo no tronco principal, não teriam necessariamente consequências fatais, e, por vezes, também, não originavam sintomatologia anginosa em vida. A diversidade da sintomatologia e do prognóstico dever-se-ia à localização e densidade das anastomoses coexistentes, à capacidade contráctil do coração. A morte seria, mais tarde ou mais cedo, o episódio final da maior parte dos casos de obstrução coronária, por ruptura da parede, assistolia súbita ou falência cardíaca.

Também Osler fizera notar, nos primeiros anos do século XX, que o enfarte agudo do miocárdio era antecedido por pródromos que alertavam para uma situação não comum (para o doente) referida à zona precordial [2]. A dor precordial foi posteriormente analisada através de estudos seriados, em doentes com enfarte agudo do miocárdio, que a validaram como sinal importante na detecção da doença [3-5].

Cerca de 200 anos antes destes últimos trabalhos, uma situação relacionada com enfarte de miocárdio fora apresentada por William Heberden, clínico e académico londrino, em artigo publicado no *Medical Transactions of the Royal College of Physicians* [6]. Naquele trabalho referente a um estudo de vinte anos, Heberden deu destaque à sintomatologia dolorosa precordial que

Myocardial infarction was first described as a clinical entity by the American physician James B. Herrick in 1912 [1]. The clarity of his observations and the rigor of his reasoning underlie many of the concepts that are still current in the pathophysiology and treatment of myocardial ischemia. It is also due to him that electrocardiography was first used systematically in the diagnosis and monitoring of patients with myocardial infarction, which became routine practice a few decades later.

According to Herrick, based on what he observed in his own patients and on late 19th-century clinical and experimental descriptions, the pathology was the result of sudden obstruction of the coronary arteries by thrombi. He also confirmed that severe obstruction of the de-scending branch of the left coronary artery was a frequent cause of sudden death; obstruction of other branches, even of the left main coronary artery, did not necessarily have fatal consequences, or even, in some cases, give rise to angina. Differences in symptoms and prognosis were due to the location and density of coexisting anastomoses and the contractile capacity of the heart. In most cases of coronary obstruction, death would occur sooner or later, caused by wall rupture, sudden asystole or heart failure.

In the early 20th century, Osler also noted that acute myocardial infarction was preceded by prodromes that alerted the patient to an unusual situation in the chest area [2]. Chest pain was later studied in series of patients with acute myocardial infarction, which confirmed its importance in detecting the condition [3-5].

Almost 200 years before these studies, a clinical setting related to myocardial infarction was presented by William Heberden, a London physician and academic, in an article published in the *Medical Transactions of the Royal College of Physicians* [6]. In this study covering a period of 20 years, Heberden highlighted the chest pain he observed, among other symptoms, in 20 patients. The pain (or chest discomfort) presented varying characteristics, intensity and frequency; however, the pain's location, its predominantly constrictive nature and the fact that it caused anxiety in its sufferers meant that Heb-erden considered it not inappropriate to term the entity "angina pectoris".

Although Heberden made no suggestions as

observara, entre outras queixas, em vinte doentes. As dores (ou sensação de desconforto précordial) apresentavam características, intensidade e frequência variáveis; contudo, a localização das dores, as suas características predominantemente constritivas e o facto de gerarem ansiedade nos portadores justificaram que Heberden considerasse não ser «desadequado» atribuir aquela entidade a denominação de angina *pectoris*.

Embora não apresentasse sugestões para a etiologia ou mecanismo daquela situação, Heberden legou um conjunto de recomendações terapêuticas, tais como a ingestão de vinho, bebidas espirituosas e ópio para alívio das dores (e, antes de deitar, para prevenção das crises nocturnas). É de referir que as três soluções terapêuticas mais utilizadas na época - sangria, vómito e purga – foram francamente desaconselhadas por Heberden.

No conjunto das observações que apresentou em 1802 no capítulo intitulado *pectoris dolor* do seu livro *Comentaries on the History and Cure of Diseases* [7], Heberden descreveu meticulosamente a sintomatologia e a evolução intermitente, com agravamento crónico progressivo, que verificara num conjunto de cerca de 100 doentes, em que se incluíam três mulheres e um rapaz com doze anos de idade. O carácter intermitente da sintomatologia, sem qualquer queixa no intervalo das crises, em que os doentes estavam aparentemente bem, constituiu para Hederden um motivo de perplexidade. Nas situações mais graves ou avançadas a crise dolorosa poderia ser desencadeada por qualquer estímulo banal e, mesmo, por «perturbações do pensamento». Outro pormenor que lhe mereceu destaque foi o da doença poder durar muito tempo, desde que não houvesse outra causa de alteração da saúde, «morrendo os doentes quase imediatamente depois de queda por desmaio súbito».

As oito características que Hederben requeria para a angina pectoris não desmerecem das descrições mais contemporâneas. Porém, é de salientar que Heberden não relacionou aquela patologia com o coração porque o «pulso não variava durante as crises», o que foi motivo para uma prolongada polémica com Caleb Hillier Parry, jovem mas já promissor clínico de Bath. Parry

to its etiology or underlying mechanism, he did put forward a series of therapeutic recommendations, such as taking wine, spirits and opium to relieve the pain and, before retiring, to prevent episodes during the night. It should be noted that the three most popular therapeutic approaches at the time – bleeding, vomiting and purging – were specifically advised against by Heberden.

In his observations published in 1802 in the chapter on *pectoris dolor* in his book *Commentaries on the History and Cure of Diseases* [7], Heberden meticulously described the symptoms and intermittent evolution, with chronic progressive worsening, that he had observed in a group of around 100 patients, which included three women and a 12-year-old boy. The intermittent nature of the symptoms, with the patients apparently well and asymptomatic between episodes, puzzled Heberden. In more severe or advanced cases, an episode of pain could be triggered by the slightest stimulus, even "any disturbance of mind". A further detail he noted was that the disease could last a long time, as long as there were no other change in the patient's health, but that eventually "the patients all suddenly fall down, and perish almost immediately."

The eight criteria that Heberden stipulated for a diagnosis of angina pectoris would not be out of place in more modern descriptions. However, it should be noted that Heberden did not relate the condition to the heart, since "pulse did not vary during the episodes", which sparked a prolonged dispute with Caleb Hillier Parry, an up-and-coming physician from Bath. Parry argued that episodes of "syncope anginosa" occurred at rest and were associated with bradycardia, preceded by feelings of anxiety and chest pain [9].

In the meantime, a patient who died with symptoms of angina was autopsied by Edward Jenner, then a country doctor in Berkeley in Gloucestershire, England [10]. Jenner, who was to become famous for his development of the method of vaccination against smallpox (the principles of which are still in use today), observed that the dead man's coronary arteries were calcified, while the rest of the heart showed no abnormalities. In a letter to Parry, his younger colleague and friend, which the latter quoted in

defendia que as crises de «síncope anginosa» ocorriam em repouso, associadas a períodos de bradicardia e precedidas de uma sensação de ansiedade ou dor precordial [9].

Sucedeu, entretanto, que um doente falecido com sintomatologia anginosa foi autopsiado por Edward Jenner, então médico de província em Berkeley, um condado de Gloucester, também em Inglaterra [10]. Jenner, que ficaria famoso pela descoberta do método de vacinação contra a varíola (cujos princípios são ainda utilizados presentemente), verificou que as artérias coronárias do falecido estavam calcificadas, enquanto o restante coração não parecia evidenciar anomalias. Numa carta que escreveu a Parry, seu colega mais novo e amigo, que este referiu em 1799 no seu livro *An Inquiry into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris* [9], Jenner relatou-lhe a descoberta de modo quase anedótico:

«... Another case (of angina pectoris(... fell under my care. In that, after having examined the more important parts of the heart, without finding any thing by means of which I could account either for his sudden death, or the symptoms preceding it, I was making a transverse section of the heart pretty near its base, when my knike struck against something so hard and gritty, as to notch it. I well remember looking up to the ceiling, which was old and crumbling, conceiving that some plaister (sic(had fallen down. But on further scruting the real case appeared: The coronaries were become bony canals. Then I began a little to suspect...».

Aquela observação fez Jenner suspeitar de que a doença anginosa e a morte-súbita que frequentemente lhe sucedia eram o resultado de uma obstrução de uma ou mais artérias coronárias. Esta opinião foi partilhada por Parry, ao anotar [9]: *«... que a causa principal da síncope anginosa existiria em alterações da artéria coronária...».*

A suspeita foi confirmada na autópsia de outro doente falecido com angina pectoris, que revelou idêntica obstrução coronária. Jenner nunca publicou aquelas importantes observações por lealdade para o seu mentor e amigo John Hunter, professor em Londres e um dos mais famosos anatomistas e cirurgiões de Inglaterra do século XVIII. John Hunter sofria de crises anginosas, pelo que Jenner não quis

his 1799 book *"An Inquiry into the Symptoms and Causes of Syncope Anginosa, commonly called Angina Pectoris"* [9], Jenner tells the story as follows:

"Another case (of angina pectoris... fell under my care. In that, after having examined the more important parts of the heart, without finding any thing by means of which I could account either for his sudden death, or the symptoms preceding it, I was making a transverse section of the heart pretty near its base, when my knife struck against something so hard and gritty, as to notch it. I well remember looking up to the ceiling, which was old and crumbling, conceiving that some plaister (sic) had fallen down. But on further scrutiny the real case appeared: The coronaries were become bony canals. Then I began a little to suspect...".

These findings led Jenner to suspect that angina and the sudden death that often followed resulted from obstruction of one or more coronary arteries. Parry was of the same opinion, noting that "a principal cause of the syncope anginosa is to be looked for in disordered coronary arteries" [9].

These suspicions were confirmed on autopsy study of another patient who died with angina pectoris, which revealed similar coronary obstruction. Jenner never published these important observations out of consideration for his mentor and friend John Hunter, a professor in London who was one of the most famous anatomists and surgeons in 18th-century England. Hunter suffered from anginal attacks and Jenner did not want his findings to worry him, and so he merely informed Hunter's doctors. They however took little notice, and indeed had no effective therapeutic measures available. Hunter died at the age of 65 from what was presumably a myocardial infarction, following a particularly stormy meeting at the hospital. The autopsy report, prepared by his brother-in-law Everard Home, did not mention obstruction of the coronaries by thrombi, although according to Livesley's interpretation [11] there was evidence of coronary and cerebrovascular disease resulting in ossification of the vessels:

"... the pericardium was very unusually thickened which did not allow it to collapse upon being opened...

The heart itself was very small, appearing too

que a sua descoberta o preocupasse, limitando-se por isso a comunicar a informação aos médicos que tratavam o doente, sem que estes, porém, a valorizassem (na verdade, também não dispunham de meios terapêuticos eficazes para o fazerem). De facto, John Hunter que veio a falecer com 65 anos de idade do que terá sido um enfarte do miocárdio, depois de uma reunião tempestuosa que havia tido no hospital. No relatório da autópsia, elaborado pelo seu cunhado Everard Home, não foram referidas coronárias obstruídas por trombos embora, conforme se lê da transcrição de Livesley [11], houvesse evidência de doença coronária e cerebrovascular, em que os vasos estariam ossificados:

«... the pericadium was very unusually thickened which did not allow it to collapse upon being opened...

The heart itself was very small, appearing too little for the cavity in which it lay.... There were no coagula in any of its cavities.... The coronary arteries had their branches which ramify through the substance of the heart in the state of bony tubes which were with difficulty divided by the knife, and their transverse sections did not collapse, but remained open.... The semilunar valves of the aorta had lost their natural pliancy, the previous stage to becoming bone, and in several spots there were evidence ossifications.

The aorta immediately beyond the semilunar valves, had its cavity larger than usual, putting on the appearance of an incipient aneurism; this unusual dilation extended for some way along the ascending aorta, but did not reach as far as the common trunk of the axillary and carotid artery. The increase of capacity of the artery might be about one-third of its natural area; and the internal membrane of this part had lost entirely the natural polish, and was studded over with opaque white spots, raised higher than the general surface....

... but the internal carotid arteries, as they pass by the sides of the sella tursica, were ossified, and several of the ramifications which go off from them had become opaque and unhealthy in their appearance. ...»

Em 1842 Marshall Hall admitiu que a causa da morte súbita nos doentes com angina pectoris ou síncope anginosa seria uma consequência da interrupção da circulação

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In 1842, Marshall Hall came to the conclusion that the cause of sudden death in patients with angina pectoris or syncope anginosa was the result of interruption of the coronary circulation [12].

Interestingly, the first known description of a condition suggestive of angina pectoris was in the previous century, in the autobiography of Edward Hyde, a Member of Parliament and high-ranking official at the court of the English king Charles II in the 17th century. Although he was not a physician, Hyde described his father's illness in detail until the latter's sudden death in 1632 [13].

It should be noted that Hyde's description and Heberden's observations received little or no attention in medical circles in the following centuries. Similarly, the thrombogenic theory of myocardial infarction proposed by J. B. Herrick also went almost unnoticed in his time.

In 1915, Clifford Allbutt, a highly respected figure in the English medical community, was still convinced that angina pectoris originated in the aorta [14]. In a study published in 1918 of 200 cases of angina pectoris, Herrick and

coronária [12].

Curiosamente, a primeira descrição conhecida de uma situação sugestiva de angina pectoris havia sido referida no século anterior, na auto-biografia de Edward Hyde, parlamentar e alto dignitário da corte inglesa de Charles II no século XVII. Hyde, apesar de não ser médico, descreveu em pormenor a doença do seu pai, até este falecer subitamente, em 1632 [13].

É de notar que a história contada por Hyde assim como as observações de Heberden foram pouco ou nada valorizadas em contexto médico nos séculos seguintes. Igualmente, a teoria trombogénica do enfarte de miocárdio, apresentada por J. B. Herrick, passou quase despercebida no seu tempo.

Em 1915 Clifford Allbutt, autoridade médica conceituada da medicina inglesa, ainda defendia que a angina pectoris tinha origem na aorta (14). Num estudo publicado em 1918 sobre 200 casos de angina pectoris, Herrick e Nuzum referem a possível origem aórtica da angina em cinco doentes que também tinham insuficiência aórtica o que, pelos conhecimentos actuais, poderia resultar do colapso da artéria coronária durante a fase diastólica de enchimento [15]. A génese do enfarte de miocárdio por trombose coronária foi reanalisada por Herrick em 1919 [16].

O conceito, actualmente aceite, de que a sintomatologia da angina pectoris resulta do fornecimento insuficiente de sangue ao miocárdio, foi proposto por Mackenzie em 1923 (17) e confirmado por Coombs em 1930, o qual também associou aquele mecanismo ao enfarte de miocárdio [18]. Gradualmente, a noção de que existiria uma causa comum a ambas as situações ganhou aderentes.

Em 1971 Braunwald consolidou as bases fisiopatológicas de controlo do consumo de oxigénio pelo miocárdio, em relação com as exigências metabólicas e o fluxo de perfusão sanguínea nas coronárias [19].

De acordo com as observações de Livesley e Oram, em 1973, o quadro clínico da angina sobrevém quando determinadas regiões do miocárdio ficam em estado de isquémia, sendo esta subsequente a um menor fornecimento de oxigénio relativamente às maiores quantidades exigidas pelo sector afectado. A sintomatologia desapareceria, em geral, com o repouso e a

Nuzum proposed a possible aortic origin of the angina in five patients who also had aortic regurgitation; current understanding suggests this could be due to collapse of the coronary artery during the diastolic filling phase [15]. The genesis of myocardial infarction due to coronary thrombosis was re-examined by Herrick in 1919 [16].

The idea, now accepted, that the symptoms of angina pectoris are caused by inadequate blood supply to the myocardium was proposed by Mackenzie in 1923 [17] and confirmed by Coombs in 1930, who also associated it with myocardial infarction (18). The notion of a common cause underlying both conditions gradually gained ground.

In 1971, Braunwald provided evidence of the pathophysiological basis of control of myocardial oxygen consumption depending on metabolic demands and blood flow in the coronary arteries [19].

The observations of Livesley and Oram in 1973 showed that the clinical setting of angina arises when certain areas of the myocardium become ischemic, as a result of the oxygen supply failing to meet the increased demands of the sector affected. Symptoms would generally disappear with rest and reduction in heart rate, which would lower myocardial aerobic metabolic demands to a level compatible with the oxygen capacity of the coronary flow. A small percentage of patients would present signs of angina during periods of bradycardia. In these situations, the angina would result not from coronary obstruction but from tissue hypoperfusion and reduced coronary flow caused by an active decrease in heart rate [19, 20].

With increased life-expectancy and changes in diet, coronary atherosclerosis has become a major, and increasingly common and serious, cause of restricted blood flow to the myocardium, resulting in angina and myocardial infarction [21].

diminuição da frequência cardíaca, que reduziriam as necessidades do metabolismo aeróbio do miocárdio a um nível compatível com as possibilidades de oxigenação do fluxo coronário. Um grupo mais restrito de doentes apresentaria indícios de angina em períodos de bradicardia. Nestas situações, a ocorrência não resultaria da obstrução coronária mas da hipoperfusão tecidual e redução do fluxo coronário, por diminuição activa da frequência cardíaca[19, 20].

Com o aumento da longevidade e a

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