

Living with pain



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In this issue of *Heart & Metabolism*, our attention is focused on the challenging clinical condition of refractory angina. William Heberden's classic description of angina pectoris was first presented to the Royal College of Physicians in 1768 and a few years later published in the *Medical Transactions* of the College. Although receiving praise for his detailed description of the symptoms accompanying the natural history of patients with exertional angina, Heberden humbly acknowledged that "with respect to the treatment of this complaint, I have little or nothing to advance." Exactly two and a half centuries later, we are awed by the great developments we have witnessed in the treatment of patients with stable angina, ranging from effective antianginal drugs to revascularization procedures (percutaneous or surgical). But despite all the advances, we are occasionally faced with a patient with disabling symptoms related to myocardial ischemia and who becomes unresponsive after an initial course of medical therapy. To make things worse, because of the anatomical complexity of the disease, including the diffuseness of the obstructive lesions, or because the patient is considered high risk, the Heart Team deems that revascularization is unsuitable, and the patient is said to have refractory angina. What happens then? The articles in this issue will give the reader a broader, updated, and (hopefully) uplifting perspective on the topic.

We start our journey questioning the definition of refractory angina in light of what is known regarding the multiple pathophysiological mechanisms involved in angina or myocardial ischemia. After reading the article by Dr Huqi and Prof Marzilli, it becomes clear that one must first understand the underlying mechanism responsible for the clinical manifestations of any

disorder in order to propose an adequate therapeutic strategy. In the setting of stable angina, failing to adhere to this recommendation may lead not only to misuse of currently available pharmacological therapies, but also to overuse of myocardial revascularization procedures. In the end, many patients with apparent refractory angina may simply be undergoing inappropriate therapy.

The difficulty in making a proper diagnosis of refractory angina may help explain the uncertainties regarding the true prevalence of refractory angina in daily clinical practice, which I discuss in a following article. Even so, the estimated incidence of patients fulfilling the criteria for refractory angina per year on both sides of the Atlantic make it clear we should be prepared for a growing population of patients with difficult-to-control symptoms.

In addition to the evident impairment in quality of life that patients with refractory angina experience, persistent angina also has prognostic implications, as discussed in the article by Prof Steg. Large, contemporary registries have shown that the presence of angina and/or myocardial ischemia identifies patients at higher risk for cardiovascular events, including cardiovascular death and/or myocardial infarction. Thus, our mission has been expanded, aiming to improve symptoms *and* to reduce the cardiovascular risk in patients with angina and/or ischemia. As a welcomed complement to the topic, the Refresher Corner article by Prof Di Carli and Prof Agarwal presents the many clinical tools at our disposal for estimating ischemic burden. Thanks to these tools, ischemia is no longer a dichotomous variable (present/absent), but rather a quantifiable one.

The management of patients with refractory angina may seem, at first, to be a dead-end road, but it is not. There is, indeed, great opportunity for medical

research to introduce new drugs and new nonpharmacological therapies for such patients. Prof Henry's article goes through the surprisingly many options in different stages of development for clinical use in the management of patients with refractory angina. Many of these technologies are not available in all countries (eg, enhanced external counterpulsation [EECP]), and many are still in early phase clinical trials (such as cell-based therapies or the implantation of a coronary sinus reducer). Nevertheless, it is a comprehensive overview that serves as proof that patients with persistent angina have not been forgotten.

No matter how fascinating it may be to look at so many different new technologies being developed to manage a patient with persistent angina, we must bear in mind Prof Marzilli's opening paper in this issue: how appropriate is antianginal therapy in a symptomatic patient? The paper by Prof Seferović and colleagues underscores the clinical benefit of treating angina directly at the level of the cardiac cell with trimetazidine. As an antianginal agent devoid of any significant hemodynamic effect, trimetazidine treats ischemia at the cellular level, regardless of the underlying mechanism of ischemia, rendering it an attractive option as add-on therapy. In line with Prof Marzilli's advice, I share a clinical case in which the wise utilization of antianginal agents with different modes of action, according to their safety profile and tolerability, was of paramount importance in offering better symptom control in a patient initially referred to us as being refractory to medical therapy.

In the final article, with a provocative title written in Latin, Dr Huqi draws our attention to the long-standing assumption that if there's angina, one should find the obstruction and get rid of it. With few, but strong, arguments, she does show us that the relationship between a coronary stenosis and myocardial ischemia is not always direct, meaning that we may have patients with angina and no obstructive coronary disease, and that, conversely, we may find patients with obstructive coronary disease and no angina/ischemia. It's past time to rethink the "plumber theory" when treating a patient with stable angina.

I run a clinical program at the Heart Institute in São Paulo, Brazil for patients with refractory angina. I listen to them talking about what it is like to live with pain without any apparent perspective of relief. They live in fear and distress. They refrain from any physical effort; socialization is impaired. They have high rates of depression and anxiety. Editing this issue reminded me that just because something has never been done before, it does not mean it can't be done. Clinical scientists are moved and touched by patients' demands, and together with our colleagues from basic research, we all come together in search of a better understanding of the task at hand and, with that, solutions that at present are elusive.

If I could reply to William Heberden on the treatment of patients with stable angina, I'd tell him, "With respect to the treatment of this complaint, I have so *much* to advance."

I hope you enjoy the reading as much as I have. ■