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Changing epidemiology of ischemic heart disease

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Over the last 30 years considerable progress has been made in the treatment of ischemic heart disease (IHD). However, population studies confirm that the problem is far from being solved, and IHD remains the leading cause of morbidity and mortality in industrialized countries.

Several factors limit the efficacy of available treatments, including major changes in the clinical profile of ischemic patients. Compared with the past, today’s patients tend to be older, to have undergone revascularization procedures, and more often to have co-morbidities, including heart failure and diabetes.

Patient age

The prevalence of coronary artery disease (CAD) increases with advancing age, representing the major cause of mortality, morbidity, and disability in the elderly. Elderly patients have a higher incidence of multi-vessel coronary disease, and often show a decrease in left ventricular function. Furthermore, elderly patients are often excluded from revascularization procedures, leaving medical treatment as the only therapeutic resource. Unfortunately, in the elderly, there is a higher risk of drug interaction, and a higher incidence of adverse effects due to altered pharmacokinetics secondary to renal and hepatic dysfunction. Compliance is also a common issue with older patients.

Diabetes

The prevalence of diabetes is growing rapidly. From 1994–2002, the age-adjusted prevalence of diabetes increased 54.0% for adults (from 4.8% to 7.3%) in the United States. The prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and a projected 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. In diabetics, coronary revascularization procedures have been shown to have a lower success rate and a higher rate of complications than in non-diabetics, again stressing the need for more effective drugs.

Heart failure

Heart failure (HF) incidence approaches 10 per 1,000 in the population after age 65. About 22% of male and 46% of female heart attack (MI) victims will be disabled with HF within 6 years, including patients revascularized in the acute phase.

After HF is diagnosed, survival is poorer in men than in women, but fewer than 15% of women survive more than 8–12 years. The 1-year mortality rate is high, with 1 in 5 dying. In people diagnosed with HF, sudden cardiac death occurs at 6–9 times the rate of the general population. From 1993–2003, deaths
from HF (International Classification of Diseases code 428) increased 20.5%. In the same time period, the death rate declined 2.0%. The 2003 overall death rate for HF was 19.7%. The presence of HF limits antianginal drug selection and multiplies prescriptions, with obvious compliance problems.

**Post-percutaneous coronary intervention angina**

Patients refractory to medical treatment are eventually referred for myocardial revascularization. Revascularization procedures are expected to improve symptoms and prevent death and myocardial infarction. Unfortunately, available data do not support this common belief. According to the data from the Bypass Angioplasty Revascularization Investigation, about 30% of patients never return to work following coronary revascularization, and 15% to 20% of patients rated their own health fair or poor despite revascularization. Percutaneous transluminal coronary angioplasty (PTCA) results in superior symptomatic relief of angina compared with medical therapy, but the difference is less than expected and narrows with time. Only a minority of patients are free from angina and antianginal medications after a revascularization procedure.

These are just some of the factors explaining why tailoring therapy to individual needs has become progressively more challenging in IHD. This issue of Heart and Metabolism focuses on these issues and offers clues to how we can deal better with this challenge.
Emerging patterns in IHD in developing countries

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Abstract

In the past decade, Europe has undergone significant societal changes that include a shift of the highest premature cardiovascular mortality rate from industrialized countries to Eastern Europe. Mortality represents the most reliable indicator to estimate the burden of ischemic heart disease (IHD), and the mortality rate from IHD in Eastern Europe is higher than that of the United States and Western European countries. There are few reports regarding the incidence, mortality and quality of assistance of IHD in transitional countries. However, the recent International Survey of Acute Coronary Syndromes in Transitional Countries, a large international investigative effort that will evaluate the role of evidence-based therapies and interventional cardiac procedures over a three-year period, may help to improve clinical outcomes in these countries.

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Keywords: Epidemiology, Europe, ISACS-CT, ischemic heart disease, MONICA

Introduction

Ischemic heart disease (IHD) is the leading cause of mortality and morbidity in the United States and Europe [1,2]. It represents a tremendous financial burden, which is related to the cost of healthcare and social services, illness benefits and retirement, as well as its impact on families and caregivers, and loss of productive life years.

When describing the epidemiology of cardiovascular disease and its risk factors in Europe, one must remember that the political and economic profile of Europe has undergone extraordinary changes in the past two decades. In Eastern Europe and the former Soviet Union, changes in patterns of health differ greatly from those found in Western Europe. Today, the European region comprises 53 countries. Each of these countries has its own political, economic, and cultural history that has had specific influence on cardiovascular epidemiology. Social, economic and cultural factors play a crucial role in determining a disease found so frequently in the population, and this becomes evident when evaluating data on health; in these countries, societal changes have had a significant impact.

Mortality represents the most reliable indicator to estimate the burden of IHD in Europe. It allows a number of comparisons to be made regarding the several aggregates of European countries, and these observations are quite insightful to contextualize the epidemiology of coronary artery disease (CAD) in Europeans.

Mortality rate of ischemic heart disease

Tatu-Chitoiu et al. recently reported the in-hospital mortality rate in more than 9,000 patients admitted to hospitals in Romania with acute ST-elevation myocardial infarction. Compared to the standard in Western countries, the study showed a low rate of use of standard types of care (e.g., thrombolysis) and of newer treatments, such as primary percutaneous
coronary intervention [3]. The in-hospital mortality rate for patients with acute ST-elevation myocardial infarction in the registry was 12.7% as compared with the Euro Heart Survey (< 7%) [4] and the United States National Registry of Myocardial Infarction (8%) [5]. This study reported that, in Romania, inadequate acute medical care contributed not only to high in-hospital mortality, but also to overall mortality from coronary artery disease.

Another experience among multicenter centers in various countries throughout the world involved the World Health Organization’s Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project, which promoted the detection of incidence and attack rates for cardiovascular events using standardized procedures, allowing a reliable comparison between units of observation [6]. Yet, analysis of this phenomenon has been hindered by insufficient information. The MONICA Project for monitoring cardiovascular mortality and risk factors considered only six Eastern European countries—Russia, Yugoslavia, Poland, Czechoslovakia, Hungary and the former East Germany. This international registry confirmed that the mortality rate from IHD in Eastern Europe is higher than that of the United States and Western European countries [7].

**Difference in coronary risk factors**

In recent years, mortality from cardiovascular disease has been decreasing continuously in the United States and in many Western European countries. However, during the last decade, the region with the highest premature cardiovascular mortality rate has shifted from industrialized countries to Eastern Europe. In recent years, Latvia, Estonia, the Russian Federation, and Hungary have had the highest cardiovascular mortality rates. This increased risk of mortality is only partially explainable by the high prevalence of traditional risk factors. The MONICA surveys have shown that there were no substantial differences between Eastern Europe and democratic countries regarding the prevalence of traditional risk factors (dyslipidemia, diabetes, and hypertension), with the significant exception of male smokers. Smoking and alcoholism are definitely important risk factors, but additional local risk factors in Eastern Europe need to be identified with more specific target-prevention programs in individual Eastern Europe countries [8]. There are no data, however, regarding the role of food, antioxidant vitamins and inflammation in these countries.

**Possible explanation**

The failure of economic and political systems to satisfy material and psychosocial population needs has probably been an important factor in the cardiovascular disease epidemic in Eastern Europe.

The MONICA data suggest that poor quality of care contributed to the high mortality rate from coronary artery disease in Eastern Europe. However, in these analyses, it was difficult to separate the effects of the quality of care from those of CAD risk factors and socio-economic characteristics [6].

In the more economically stable countries, both IHD and stroke mortality are declining, whereas one can note two key characteristics in countries that are less economically stable: (a) the morbidity and mortality rates are higher, and (b) secular trends show a fluctuation with an early increase and a recent tendency towards a small decrease, an indicator of the influence the disordered and rapid change of living conditions has had on these populations. A comparison of populations under the age of 65—which includes the potential working life span-representative of various geo-socio-political parts of Europe shows a four- to six-fold difference in coronary heart disease and stroke mortality rates in recent years in countries with different economic conditions.

However, important limitations need to be considered when comparing the mortality rate between former Communist and Western countries, because the mortality rate depends on the length of hospital stay, health assistance, and post-discharge assistance. Another limitation may be that Eastern Europe patients may have phenotypes that may not be comparable with other populations. Finally, the presence of other comorbidities or differences in diagnostic practice may influence the prognosis in IHD.

**The International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-CT)**

The International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-CT) is both a retrospective (over a one-year period) and prospective (over a three-year period) study that was designed to obtain data about patients with acute coronary syndrome in countries with an economy in transition, and thereby control and optimize internationally recommended guideline therapies in these countries [9]. There are a total of 132 collaborating centers in ten transitional countries (Bulgaria, Croatia, Hungary, Poland, Russian Federation, Romania, Serbia/Montenegro, and Ukraine), and a total of 30 centers in five industrialized countries (Italy, Greece, Finland, the United Kingdom, and the United States) that serve as control.
The survey has four aims: (1) documenting the characteristics of all patients presenting to the enrolled centers with ST-segment-elevation myocardial infarction (STEMI) or non-ST-segment-elevation myocardial infarction (NSTEMI), (2) documenting in-hospital outcome and outcome rates at 6 months and 1 year, (3) documenting interventional cardiac procedures and related complications, and (4) documenting therapeutic regimens and investigating conformity of treatment with already established guidelines. The survey encourages optimal evidence-based therapies, and the international patient body ensures good representation of multiple practice patterns.

Conclusion

There are few reports regarding the incidence, mortality, and quality of assistance of IHD in transitional countries. Moreover, in other European areas, the size of these phenomena can be estimated based on local observations. The only international registry was the MONICA Project, which enrolled patients from 1989 to 1999 and did not take into consideration the most recent knowledge regarding the pathophysiology of IHD and cardiac risk factors [8]. ISACS-CT is a large international investigative effort that will evaluate the role of evidence-based therapies and interventional cardiac procedures over a three-year period. It may help to additionally improve clinical outcomes in countries with an economy in transition.

REFERENCES


Abstract

There have been significant advances in the definition, diagnosis, and management of acute coronary syndromes over the past decade. The roles of both medical management and revascularization have been examined in several large scale randomized controlled trials. As such, the management of ST-segment elevation myocardial infarction is well established. Until this year, agreement over the most appropriate management of non-ST segment elevation myocardial infarction also seemed close, but the recent publication of the 5-year follow-up of the Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial seems to have again cast doubts over current practice. Here, we explore the current practice and future management of acute coronary syndromes.

Introduction

Over the past decade, significant advances have been made in the care of patients with acute coronary syndromes (ACS). The improvements encompass diagnosis (cardiac biomarkers, non-invasive angiography, functional imaging), management (medical and revascularization), and secondary prevention. Despite these advances, the best early management of the largest class of ACS (non-ST-segment elevation myocardial infarction [NSTEMI]) remains uncertain. In this review, we explore the pathophysiology, current best management, and future perspectives of the acute coronary syndromes.

Pathophysiology of acute coronary syndromes

ACS arise due to inadequate oxygen supply to the myocardium and can be attributed to five interacting variables: thrombosis, mechanical obstruction, dynamic obstruction, increased myocardial oxygen demand and inflammation or infection [1], but the formation of atherosclerotic plaques within coronary arteries underlies most ACS. Plaque formation is the result of a chronic immune-inflammatory process driven by lipid accumulation within the walls of medium-sized and large arteries. This causes either gradual luminal narrowing leading to a relatively fixed and irreversible lesion or rapid and potentially reversible occlusion as a result of thrombosis [2], vasospasm [3], or both. Atherosclerotic plaques initially form as precursor lesions, known as fatty streaks, which appear in infancy. The transition from these benign lesions to plaques prone to rupture is a continuous process with relative phases of stability and instability. Unstable plaques typically have a large lipid core, a high concentration of inflammatory cells and a thin fibrous cap [4]. Triggered by multiple patient-specific genetic and environmental factors, the final common pathway of plaque rupture, exposure of the necrotic prothrombotic core and coagulation cascade activation [5] leads to intraluminal thrombosis and ACS.
**STEMI or NSTEMI: who decides?**

Myocardial infarction (MI) has historically been defined as a combination of two of three characteristics: typical symptoms, a typical ECG pattern with development of Q waves, and a rise in cardiac enzymes. This definition became outdated in terms of risk stratification and lagged behind the development of new diagnostic techniques. The European Society of Cardiology/American College of Cardiology/American Heart Association (ESC/ACC/AHA) consensus conference of 1999 [6] therefore re-classified ACS based on the presence or absence of ST elevation and the subsequent detection of necrosis, whether that be via electrocardiographic, biochemical, pathological, or imaging modalities. Patients without ST elevation during the acute phase and without Q wave development could now be classified as MI, with wide-ranging therapeutic and epidemiological implications. The terminology for MI developed by the conference has been adopted with ACS now classified as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA), in which there is no evidence of myocardial necrosis.

The clinical entities of STEMI and NSTEMI also differ in the underlying pathological processes and the relative contributions of thrombus formation and vasospasm (Figure 1). STEMI is usually associated with complete vessel occlusion [7] and unstable angina or NSTEMI with subtotal occlusion [8]. The components of the thrombus have also been found to be different in patients with STEMI compared to those with NSTEMI [9]. The former is predominantly fibrin-rich and the latter platelet-rich.

The importance of the ability to classify a proportion of ACS as MI that were previously attributed to unstable angina can be seen in both the prevalence and mortality statistics. In the United States, unstable angina and NSTEMI account for over four times the number of admissions to hospital than STEMI [10] and despite STEMI having a worse 30-day mortality than NSTEMI, they have similar 1-year [11] and 5-year mortality rates [12]. Although hospitalization rates due to MI remain largely stable, the proportion of STEMI does seem to be falling while that of NSTEMI appears to be increasing [13]. One hypothesis for the changing epidemiology of STEMI/NSTEMI is that treatment and prevention strategies are largely directed toward plaque disease and thrombosis, and not toward other important factors involved in the pathogenesis of NSTEMI (Figure 1). Alternatively, better reporting arrangements to large national registries may reveal previously unidentified cases of NSTEMI. Nevertheless, together these findings underline the importance of identifying best-practice management of NSTEMI.

**Management of STEMI**

Treatment for STEMI has evolved over the past 30 years with the advent of thrombolysis, percutaneous coronary intervention (PCI), and the optimization of medical therapy. The survival benefit achieved from relieving coronary obstruction by thrombolysis was demonstrated in 1988 by the Second International Study of Infarct Survival (ISIS-2) trial, with the survival benefits of aspirin and streptokinase extending to 10-year follow-up [14]. The concept of a “golden hour” in which early intervention provides improved myocardial rescue was confirmed in an analysis of 22 trials comparing thrombolytic therapy to placebo [15]. This analysis found that presentation within 2 hours of symptom onset led to substantially higher benefit from thrombolysis, showing that efficient triage and early intervention improves mortality.

Primary PCI then emerged as a treatment strategy, with a meta-analysis of ten randomized trials [16] comparing primary coronary angioplasty with intravenous thrombolysis finding a 34% reduction in 30-day mortality in the angioplasty group with an associated reduction in stroke and re-infarction. The improved mortality, re-infarction and re-admission rates of PCI were also evident over pre-hospital thrombolysis, and extended to 1-year follow-up [17]. In addition to thrombolysis and PCI, many trials have considered what medications confer a survival benefit post MI. Antithrombotic agents, beta-blockade, inhibitors of the renin-angiotensin system, and lipid-lowering medications have all shown a survival benefit if used in an appropriate context.

Several trials have examined a “pharmaco-invasive” strategy, whereby patients presenting with STEMI in non-PCI centers are treated with half dose thrombolysis before urgent transfer to a PCI center. The Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI) trial...
Main Clinical Article

The changing face of acute coronary syndromes

Management of NSTEMI

As for STEMI, medical management of NSTEMI with anti-ischemic agents (beta-blockers, nitrates) and antithrombotic agents (aspirin, heparin) is well accepted. However, the role and timing of invasive reperfusion techniques in NSTEMI remains less clear. In stark contrast to the results of thrombolysis in STEMI, thrombolysis was early shown in TIMI-IIIB to lead to harm (increased fatal and non-fatal MI) in patients without ST-segment elevation [23]. This trial, from 1994, also compared the role of “early invasive” versus “early conservative” strategies in the management of “non-Q-wave myocardial infarction”, and found no difference in subsequent rates of death, myocardial infarction, or angina. Subsequently, there have been many large trials comparing these two strategies and still an overall consensus has not been reached.

In the “early invasive” strategy, angiography is typically performed prior to hospital discharge, while in the “early conservative” strategy, best medical management is followed by angiography as indicated by symptoms or recurrent ischemia on provocative testing. Excluding patients with hemodynamic or electrical instability who require immediate angiography, current guidelines recommend risk-stratifying patients with NSTEMI and following an early invasive strategy in those with intermediate to high risk of further events [9,24]. While the European guidelines [9] do recommend against routine angiography in low-risk patients, the American guidelines [24] only recommend limiting the use of angiography in patients with significant co-morbidities, low likelihood of cardiac chest pain, or unwillingness to consent to revascularization. The difference is subtle, but suggests agreement over those patients that should receive early intervention, but not those that are less likely to benefit.

In theory, the early invasive strategy will lead to revascularization (PCI or coronary artery bypass grafting [CABG]) being performed earlier than the early conservative strategy. This supposed advantage must be weighed against the procedural complications and cost in performing greater numbers of invasive procedures. What then is the trial evidence for and against the invasive strategy? In addition to TIMI-IIIB, several other randomized controlled trials (Veterans Affairs Non-Q-wave Infarction Strategies in Hospital [VANQWISH] trial [25], the Medicine versus Angiography in Thrombolytic Exclusion Strategies in Hospital [MATES] trial [26], the Facilitated Intervention for Coronary Revascularization Versus Angiography in NSTEMI [FACTS-2] trial [27]) have favored a conservative approach. In VANQWISH there was no difference in death or non-fatal MI between the invasive and conservative arms, and patients randomized to the invasive arm had worse clinical outcome up to 1 year. In MATE, despite revascularization occurring earlier and more often in the invasive group, there was no difference in death or non-fatal MI at 1 year. In RITA-2, there was an improvement in severe angina in the intervention group, but there was also excess mortality in the intervention group, attributed to peri-procedural myocardial infarction. More recently, in ICTUS [28] there was a significantly decreased rate of rehospitalization but an increased rate of subsequent myocardial infarction in the interventional arm. This trial is important since it utilized aspirin, heparin and glycoprotein IIb/IIIa inhibitor (GPI) and encouraged the use of clopidogrel and statins and hence mirrors most closely current best medical management.

While this data seems conclusive, other studies support the use of an early invasive strategy. The Fast Revascularization with InStent Restenosis (FRISI-II) [29] and Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI 18) [30] demonstrated fewer deaths and non-fatal myocardial infarctions in the invasive arms. RITA-3 [31] identified a reduction in refractory angina, but failed to show an improvement in mortality. There were significant
methodological advantages of RITA-3 over the two prior studies, especially that the definition of myocardial infarction did not differ in the two arms of RITA-3. In FRISC-II and TACTICS-TIMI 18, there were more stringent definitions of MI after PCI than after conservative management perhaps contributing to the apparent reduction in MI by early intervention. These trials also differed in the use of GPIs, with none used in FRISC-II, variable use in RITA-3, and routine use in TACTICS-TIMI 18. All three of these trials did, however, come after the development of intracoronary stents, and hence are more representative of “current-day” methods of intervention.

Factors predicting success of an invasive strategy in NSTEMI

Subsequent studies have tried to identify subgroups of patients who are likely to benefit most from the early invasive approach. The benefit of early intervention in NSTEMI may occur in men and women equally [30] or may be limited to men with high-risk features [29,32]. This may be explained by the greater severity of coronary artery disease seen in men on presentation [33]. Additionally, systolic dysfunction may represent an independent predictor of good response to an invasive strategy [34].

Another explanation for the differences between these trials is crossover between the invasive and conservative arms. For example, patients randomized to the conservative arm may undergo intervention before hospital discharge dictated by symptoms or recurrent ischemia. The proportion of such patients that effectively “cross over” to the alternate arm varies in each of the trials, making analyses extremely difficult. One approach to solving this problem is to interrogate existing databases, as was done in Global Utilization of Strategies To open Occluded coronary arteries trial IV in Acute Coronary Syndromes (GUSTO-IV ACS) [35]. In doing so GUSTO-IV ACS identified a relative risk of death in the invasive arm of almost half that in the conservative arm.

The effect of timing on outcome is also not known. In STEMI, the benefit gained from an immediate interventional approach is well recognized [22], but after the demonstration of harm arising from immediate thrombolysis in NSTEMI [23] few trials have addressed the role of immediate revascularization in NSTEMI. In the Value of First Day Angiography/Angioplasty in Evolving Non-ST Segment Elevation Myocardial Infarction (VINO) trial [36], comparison of first day intervention (at a mean time of 6.2 hours) versus a conservative strategy found reduced mortality and re-infarction at 6 months in the invasive arm. However in contrast to these results, TACTICS-TIMI 18 (in which the mean time to revascularization was 22 hours) had no effect on mortality, but FRISC-II (in which the mean time to revascularization was 4 days) did significantly improve long-term mortality. Furthermore, results from the Global Registry of Acute Coronary Events (GRACE) registry examining early access to catheter laboratories at presentation found an association between early access to intervention and increased mortality at 6 months [37].

Hence, as yet there is no consensus on the “gold standard” management of NSTEMI and although incidence of MI is falling overall, the proportion of NSTEMI is increasing. This may be due to changing population demographics with more female gender, diabetes mellitus, old age, and obesity [38], or may be related to the increased use of preventative medications or improvements in the sensitivity of cardiac biomarker assays [39]. Regardless, the impact of the above uncertainty is likely to grow as the relative prevalence of NSTEMI increases.

Future management of acute coronary syndromes

Perhaps then, the current guidelines exist as they do not because they represent the best approach, but because they represent the only approach. Risk stratification certainly can be performed repeatedly and reliably using for example the GRACE or TIMI scores, and on balance the trials above seem to support early intervention (at 4 hours to 7 days) in high-risk patients.

This year has however seen the publication of several further trials, which yet again do not reach consensus. Fox et al [40] performed a repeat analysis of the above trials (selecting FRISC, RITA-3, and ICTUS) and supported the routine invasive strategy based on reduced death or MI in high-risk patients. In contrast, the 5-year follow-up of ICTUS was also published and failed to show any benefit of a routine invasive strategy in death or MI [41]. Perhaps the future will see better selection of patients, or better timing of intervention. A meta-analysis performed by Katriris et al [42] and a randomized trial performed by Shiabasi et al [43] examined the effect of timing and seem to support rapid access to revascularization after presentation. Meanwhile the development of continuous electrocardiography may better predict subsequent mortality and therefore those patients most likely to benefit from the invasive strategy [44].

Conclusions

In summary, the past 20 years have reinforced the correct management of STEMI, but seem to have generated more questions than answers in the management of NSTEMI (Table I). Meanwhile, NSTEMI is
becoming more prevalent and hence its correct management is a key question. Due to the long lead time required to follow-up interventional randomized trials, and the rapid development of better medical and interventional therapies, it seems likely that future trials will always be one step behind the best management of the day.

Table I. Unanswered questions in the management of NSTEMI.

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Detecting acute coronary syndromes by magnetic resonance imaging

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Abstract

Only a small subset of the many patients presenting with chest pain are eventually diagnosed with acute coronary syndromes (ACS). Early identification of this high-risk group can be challenging, particularly since many will initially have non-diagnostic electrocardiograms and normal cardiac enzymes. There is, therefore, great clinical interest in new methods for better detection of ACS. A number of important recent studies using cardiac magnetic resonance (CMR) as well as new developments in CMR techniques have led to growing excitement over the possibility of using CMR to improve detection of ACS. This review will provide an overview of these developments and suggest possible uses of CMR for this indication.

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Keywords: Acute coronary syndrome, chest pain, magnetic resonance imaging, myocardial infarction, unstable angina

Introduction

Acute coronary syndromes (ACS) span a broad range of clinical presentations, including STElevation myocardial infarction, non-ST-elevation myocardial infarction (NSTEMI), and unstable angina. In the United States, more than 5 million patients per year are evaluated in the emergency department (ED) setting for chest pain or other symptoms suggestive of ACS [1]. A minority of these patients will present with significant electrocardiogram (ECG) changes and/or positive troponins requiring immediate admission and usually also cardiac catheterization. At the other end of the spectrum, a small proportion of patients will be assessed as having a very low probability of ACS based on clinical evaluation alone and be discharged early from the ED. The majority of patients, however, will be determined to have an intermediate risk for having underlying ACS. In this group, initial serologic markers are negative for cardiac injury and resting ECG changes are non-diagnostic for ACS. Although serum troponins are extremely sensitive for detecting myocardial infarction (MI), by definition, these assays do not detect unstable angina. Furthermore, the time course of troponin elevation is from a few hours to a few days after myocardial necrosis. Thus, measurements outside this time window may be negative and falsely reassuring. Finally, it is well recognized that the ECG can be completely normal in ACS. The fear of discharging someone with possible underlying ACS results in the admission of the great majority of these patients who ultimately prove to have no evidence for ACS [2]. Only about 30% of patients admitted for suspected MI are eventually diagnosed with ischemic heart disease [2]. On the other hand, up to 4% of chest pain patients discharged from the ED experience an MI within 30 days with potential fatal consequences and serious medico-legal implications [3].

Physicians thus routinely face the question of how to manage patients who present with possible ACS at initial clinical evaluation. There is, therefore, great clinical interest in new methods for better detection of
ACS. A number of important recent studies using cardiac magnetic resonance (CMR) as well as new developments in CMR techniques have led to growing excitement over the possibility of using CMR to improve detection of ACS. In this review, we will provide an overview of these developments and suggest possible uses of CMR for this indication.

**Detection of myocardial infarction**

The most accurate and best validated CMR technique for diagnosis of MI is late gadolinium enhancement (LGE) imaging. This method requires intravenous administration of gadolinium contrast followed by inversion recovery imaging after a delay of about 10 minutes [4]. Normal myocardium appears black or nullled, whereas nonviable regions appear bright or enhanced. The mechanism of the enhancement is likely based on the principle that gadolinium chelates are extracellular agents that cannot cross intact cell membranes; and in normal myocardium myocytes are densely packed thus excluding gadolinium [5]. The overall concentration of gadolinium is therefore small in normal myocardium. With acute myocyte necrosis (as in acute MI or myocarditis), there is membrane rupture, which allows gadolinium to diffuse into myocytes. This results in increased gadolinium concentration, shortened T1 relaxation, and thus leads to signal enhancement. Interestingly, in the chronic setting, the mechanism is similar with scar replacing necrotic tissue and expanding the interstitial space, leading to increased gadolinium concentration and enhancement. Extensive validation of this CMR LGE imaging technique has been done in animal models of infarction, showing a nearly exact relationship between the size and shape of infarcted myocardium by CMR LGE imaging to that of histopathology [6]. Moreover, these studies have shown that infarct size measured by CMR LGE is closely associated with peak cardiac enzyme release [7] and measurements by positron emission tomography [8]. CMR LGE has been shown to be more sensitive than singlephoton emission computed tomography (SPECT) in detecting subendocardial infarcts and infarcts in nonanterior locations [9]. Furthermore, the high spatial resolution of CMR LGE has been shown to allow detection of even microinfarcts, involving as little as 1 g of tissue such as those occurring in the context of percutaneous coronary stenting [10].

Importantly, CMR LGE is the only imaging technique to have been tested in a prospective randomized multicenter trial for detection of MI [11]. A total of 566 patients with first-time MI were scanned after cardiac catheterization in 26 centers. The study showed that the sensitivity of CMR LGE reached 99% and 94% in acute and chronic MI, respectively. Furthermore, the correct location (based on the infarct-related artery) was identified in more than 97% of patients. This shows that this imaging technique is clinically robust and can be used reliably across different centers and vendors.

**Differentiating acute from chronic MI and demarcation of the area-at-risk**

Acute and chronic MI can be difficult to differentiate with conventional imaging. Both will typically exhibit wall-motion abnormalities on echocardiography, and both cause defects on SPECT scans. Likewise, as described above, both acute and chronic MI will look identical with CMR LGE. Chronic MI is more likely to be associated with a thin wall on CMR imaging or echo, but this finding is not specific. Thus, these imaging methods cannot reliably differentiate acute from chronic MI. This distinction can be critical when evaluating a patient with possible ACS who has a history of prior MI.

Recently there has been significant interest in the detection of myocardial edema, which may be a feature of many types of acute myocardial injury. The subtle increase in water content of the myocardium may be detectable with CMR using T2-weighted imaging (Figure 1). Abdel-Aty et al suggested that T2-weighted CMR was able to differentiate acute from chronic MI with 96% specificity in a study of 73 patients with acute or chronic MI [12]. It has also been suggested that the combination of T2-weight imaging of myocardial edema and LGE can measure the myocardium at-risk and the extent of salvageable myocardium (area-at-risk minus the infarcted myocardium) [13]. T2-weighted edema may also persist for some time after ACS, in theory allowing detection after the acute event. However, black-blood T2-weighted techniques are challenged by relatively low contrast-to-noise ratio as well as intra-cavitary flow artifacts in regions of slow flow adjacent to wall motion abnormalities [14,15]. Inhomogeneities of myocardial signal intensity caused by through-plane motion or associated with the use of surface coils can exceed the subtle differences caused by acute ischemia or infarction [14,15]. There is therefore great interest in developing newer T2-weighted pulse sequences that may be more clinically robust [16].

**Detection of unstable angina in the absence of myocardial necrosis**

By definition unstable angina is not associated with myocardial necrosis and therefore is not detected by
CMR LGE. However, regional wall-motion abnormalities may suggest this diagnosis in the absence of baseline abnormalities. Unfortunately, in the ED setting, it is often not known if baseline wall-motion abnormalities existed. In addition, wall motion abnormalities are not specific to ACS and can be seen in nonischemic conditions such as cardiomyopathies as well as inflammatory or infiltrative diseases.

Combined use of different CMR techniques can provide complimentary information that can be obtained in a single examination. Both wall-motion abnormalities and resting perfusion defects may be seen with MI and unstable angina. However, the absence of LGE in that region would effectively rule out MI.

Unfortunately significant underlying coronary artery disease (CAD) can still be present in the absence of resting perfusion defects, wall-motion abnormalities, and CMR LGE. The identification of significant CAD in this setting would require additional performance of stress imaging, which can also be done with CMR. Whether this necessarily represents unstable angina as opposed to the incidental finding of CAD, however, is debatable. Thus there is interest in the possible use of T2-weighted imaging to detect the presence of myocardial edema from recent ischemia that has subsequently resolved. Given the previously mentioned technical challenges, it appears that further technical improvement is needed for T2-weighted imaging sequences to be use in reliably detecting recent resolved ischemia in the absence of LGE.

Clinical studies using CMR to detect ACS

Kwong et al. performed CMR within 12 hours of presentation in 161 consecutive ED patients presenting with chest pain but no ECG evidence for MI [17]. The CMR protocol comprised myocardial perfusion at rest, cine wall motion, and LGE imaging. The authors found a sensitivity and specificity of 84% and 85%, respectively, of a resting CMR for detecting subsequent ACS defined as 70% coronary stenosis or positive stress test within 8 weeks of the index hospitalization. In addition, all 10 cases (100%) of acute myocardial infarction in that cohort defined by elevation of serum troponins, not detected by history and physical examination and resting admission ECG, were detected by CMR imaging. Detection of regional wall-motion abnormalities was the most powerful part of the CMR study in this setting where perfusion abnormalities may be normal in between episodes of pain, and infarction may not yet be established. CMR was more sensitive than ECG, troponins, and Thrombolysis In Myocardial Infarction (TIMI) risk score and was the strongest predictor of ACS on multivariate logistic regression analysis (Figure 2). A subsequent clinical study by the same group of investigators, showed that in ED patients with chest pain, non-diagnostic ECGs and negative troponins, an abnormal adenosine CMR examination predicted with high sensitivity (100%) and specificity (93%) which patients had significant CAD during one-year follow-up [18]. Furthermore, no patients with a normal adenosine CMR study had a subsequent diagnosis of CAD or adverse outcome. Plein et al studied 68 patients presenting with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) with CMR imaging of myocardial function, perfusion (rest and adenosine-stress), viability (by LGE), and coronary artery anatomy [19]. Visual analysis of CMR was carried out. CMR imaging data from all pulse sequences were first reviewed in combination, and then in a subsequent interpreting session, analyzed individually. Comprehensive CMR analysis yielded a sensitivity of 96% and a specificity of 83% to predict the presence of...
significant coronary stenosis (>70% on cardiac catheterization) and was more accurate than analysis of any individual CMR method; CMR was also found to be significantly more sensitive and accurate than the TIMI risk score. More recently, Cury et al reported the incremental value of T2-weighted imaging in 64 consecutive patients presenting with chest pain to the ED with negative cardiac enzymes and no ECG changes suggestive of coronary ischemia [20]. They reported that adding T2-weighted imaging to a core CMR protocol of cine and CMR LGE imaging increased diagnostic accuracy in detecting ACS, primarily on the basis of improving diagnostic specificity by discriminating patients with prior MI who did not have ACS from those who did. Nevertheless, T2-weighted imaging alone failed to detect 4 of the 9 patients with unstable angina presumably related to the previously mentioned difficulties with current T2-weighted imaging sequences. Overall, CMR provided incremental value in the detection of ACS over and above traditional risk stratification with the changes detected by CMR occurring before the rise in cardiac enzymes.

Important mimickers of ACS

Myocarditis may present with symptoms similar to ACS as well as positive troponins and ischemic ECG changes. The pattern of enhancement on CMR LGE can be very useful in distinguishing this from MI [21,22]. Enhancement from MI proceeds in a wavefront from endocardium to epicardium and thus always involves the endocardium. This is in contrast to the pattern in myocarditis, which often spares the endocardium and involves the mid-myocardium or epicardium (Figure 3) [23]. Takotsubo cardiomyopathy (apical ballooning syndrome) often presents in an identical fashion to ACS. Cardiac catheterization shows nonobstructive CAD and apical motion abnormalities. The absence of enhancement on CMR LGE can differentiate this entity from apical MI [24,25].

Conclusions

There is growing evidence that CMR may provide incremental improvement in assessment of ACS in some patients. In particular, LGE CMR is regarded as the gold-standard imaging technique for detection of MI and is highly accurate, reproducible, and well validated. LGE also provides unique ability to differentiate ACS from non-coronary syndromes that mimic ACS such as myocarditis. Using multiple CMR techniques (wall-motion analysis, resting perfusion, stress perfusion) in addition to LGE has been shown to increase diagnostic utility for detection of ACS in the ED setting. Preliminary studies have reported using T2-weighted edema imaging for the detection of ischemia in the absence of MI or for the differentiation of acute from chronic MI. However, further technical improvement appears to be necessary in order for T2-weighted edema CMR imaging to perform with sufficient robustness to be used in daily clinical practice.

Clearly the initial diagnostic assessment of possible ACS will continue to be firmly based on clinical evaluation, serial ECGs, and cardiac enzymes. CMR shows promise as an additional tool in this setting. However, additional studies are required to establish the optimum patient groups who may benefit from this approach. The lack of widespread availability of CMR...
equipment and trained operators in the emergency room setting are currently limiting factors to the utility of this technique. Like other imaging modalities such as CT in this setting, CMR will need to demonstrate improved patient outcomes from its use, in terms of reducing costs or enhancing management efficiency, in large randomized studies. However, given its unique capability of characterizing multiple aspects of myocardial physiology and its non-invasiveness, further clinical investigations and technical developments are in progress.

REFERENCES


Abstract

Cardiovascular disease has been considered a disease of men, while women have been attributed a very low risk of heart disease. However, it is now recognized that heart disease is the first killer disease also in women, and they present often for the evaluation of chest pain symptoms, with stable angina constituting the most common initial presentation of cardiovascular origin. Nonetheless, for the same degree of symptoms as men, women present with less obstructive coronary artery disease. Although clinical evidence for myocardial ischemia in the absence of epicardial obstruction is not a new concept, few studies have assessed its impact on clinical outcomes. In this regard, women represent a very prototypic population subset where presence of ischemia in the absence of coronary artery disease has been associated with worse clinical outcomes.

Keywords: Coronary artery disease, gender differences, ischemic heart disease

Over the past decades cardiovascular disease has been considered a disease of men, while women have been attributed a very low risk of heart disease. However, it is now recognized that heart disease is the first killer of women, with an increase at middle age [1]. Following an acute event, women are also reported to have worse outcomes, with about two-thirds of women never fully recovering.

Despite a general decline in the incidence of myocardial infarction [2], the prevalence of angina continues to be high [3]. Compared to men, women present more often for the evaluation of chest pain symptoms [4,5], with stable angina constituting the most common initial presentation of cardiovascular origin [6].

Interestingly, available data suggest that, for the same degree of symptoms as men, women present with less obstructive coronary artery disease (CAD) [7,8], with about half of all women with chest pain undergoing coronary angiography not presenting with obstructive CAD, compared with 17% of men [9]. In an era in which the search for the “holy grail of cardiology” is directed towards obstructive CAD, these and other previous observations have led to the development of the “high rate of false positives” myth in women. Practical consequences of such an assumption are a less-detailed risk factor assessment, less referral for cardiac evaluations such as stress testing, coronary angiography and less aggressive preventive treatment (i.e., antiplatelet agents and statins) in women compared with men [10,11].

However, recent data have suggested that symptoms may be equally predictive of adverse prognosis in women and men [12]. In a large-scale population study [13], women presenting with stable angina had an increased coronary mortality relative to women in the general population and, similarly, high absolute rates of prognostic outcomes when compared to men.

The Wise (Women’s Ischemia Syndrome Evaluation) study is the largest clinical trial that has evaluated ischemic syndrome and its potential mechanism with respect to clinical outcomes in the female gender. In a sub-study analysis, women who presented with angina, non obstructive coronary arteries and evidence of ischemia at nuclear magnetic resonance spectroscopy (MRS) had increased coronary event rates as compared with women with no evidence of ischemia, irrespective of CAD extent [14]. In this cohort of WISE women with chest pain, when compared with reference WISE women with CAD, members without CAD were significantly younger (56 versus 64 years, \( P < 0.0001 \)) and had lower rates of diabetes (16% versus 38%, \( P = 0.0002 \)), hypertension (55% versus 68%, \( P = 0.02 \)), and dyslipidemia (45% versus 69%, \( P = 0.0002 \)). In another, more
recent, WISE sub-study [15], authors tried to correlate reduced coronary flow reserve (CFR) in response to intracoronary adenosine administration to mid-term clinical outcomes. They reported that an impaired response to adenosine was associated with increased risk for major adverse coronary events, even in the absence of significant obstructive CAD. The link between CFR and major adverse outcomes remained significant, regardless of the presence or absence of obstructive CAD or multiple risk conditions. There was only a borderline association of this component of coronary reactivity with CAD severity. However, among 152 women without any obstructive coronary lesion, the link between impaired coronary microvascular function and adverse outcomes remained statistically significant.

These findings suggest an obvious paradox: while angina prevalence and cardiovascular outcomes in women are similar to those inmen [16], the extent of coronary artery disease is relatively low in this patient population [17,18] when compared with men of similar age.

CAD is a widely accepted predictor of adverse clinical outcomes in the general population and its association with myocardial ischemia has been the basis for development of treatment strategies primarily focused on removal of focal coronary obstructions. Unfortunately, studies aimed at assessing the impact of removal of coronary stenosis have yielded disappointing results, both on prognosis and symptoms relief.

CAD extension and severity is also considered an important prognostic factor in women with ischemic syndrome. In a study evaluating gender differences in CAD prevalence and in-hospital mortality of stable angina patients, the risk adjusted overall response (OR) for significant stenosis was 0.34 for women compared with men (P < 0.0001) [9]. Besides being older, when compared to men, women with coronary artery disease, present more often with co-morbidities, and therefore constitute a distinct high-risk subset [19].

The WISE investigators investigated coronary vascular endothelium-dependent and -independent function using intracoronary acetylcholine and nitroglycerin, respectively, in 163 women undergoing angiography. Almost 75% of the women had mild or no angiographic CAD, and during a four-year follow-up period cardiovascular events were predicted by coronary vascular endothelial function, independently of risk factors and extent of CAD [2,15].

Findings such as augmented CAD severity in post-menopausal women have led to the common belief that estrogen may serve as a “protective agent” against atherosclerosis and, consequently, ischemic events. As a matter of fact, estrogen seems to play a relevant role in women’s cardiovascular efficiency, improving the arterial wall response to injury and inhibiting the development of atherosclerosis by promoting re-endothelialization, and limiting both smooth muscle cell proliferation and matrix deposition following vascular injury [20]. Estrogen also decreases systemic vascular resistance, improves coronary and peripheral endothelial function, and prevents coronary artery spasm in women with and without coronary atherosclerosis. Interestingly enough, intracoronary infusion of estradiol improves endothelial function and coronary blood flow in female patients, but not in male patients with coronary artery disease [21]. Moreover, estrogen modulates myogenic vascular responses by reducing the basal tone of microvessels [22].

Unfortunately, randomized studies have concluded that hormone therapy not only did not reduce cardiovascular risk in secondary prevention [23], but may even result in increased coronary events, stroke and breast cancer [24–26]. However, it has recently become clear that hormone therapy has complex biological effects, e.g., it has both anti-inflammatory and proinflammatory effects and it both activates coagulation and improves fibrinolysis [20].

These observations do not deny the prognostic relevance of CAD in cardiovascular disease which, as we know, is a systemic disease, associated with increased age and comorbidities. In this regard, women with CAD and stable angina represent a particularly ill subset of patients. However, in the premenopausal phase, women with stable angina tend to have less CAD, yet similar outcomes. Although clinical evidence for myocardial ischemia in the absence of epicardial obstruction, including metabolic, electrocardiographic, scintigraphic, and histologic findings [27–29] is not a new concept, few studies have assessed its impact on clinical outcomes. Studies in women would therefore be of particular importance for a better understanding of ischemic heart disease, with or without CAD.

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New therapeutic approaches
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Clinical benefits of trimetazidine (Vastarel® MR) in the changing scenario of ischemic heart disease

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Abstract

Despite many advances in medical therapy, ischemic heart disease (IHD) remains a major health challenge worldwide. Moreover, the prevalence of IHD is growing and physicians have to face an increasing number of challenges raised by the changing profile of the patients. Trimetazidine (TMZ) (Vastarel® MR), by specifically acting to improve cardiac energy metabolism, provides benefits complementary to those of classic hemodynamic therapy that, as a result, lead to greater clinical improvement across the wide range of ischemic heart diseases. This article addresses the relevance of a cardiac energetic approach with TMZ in the treatment of stable IHD by highlighting its major clinical benefits in several subsets of high-risk patients, who are encountered more and more frequently in everyday practice, namely patients with diabetes, left ventricular dysfunction, revascularization, and the elderly.

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Keywords: Cardiac energy metabolism, cardioprotection, diabetes, IHD, LV dysfunction, trimetazidine MR

Introduction

Despite many advances in medical therapy, ischemic heart disease (IHD) remains a major health problem worldwide. Moreover, with the aging of the population and the worldwide epidemic of diabetes, the prevalence of IHD is growing and physicians have to face an increasing number of challenges raised by the changing profile of the patients [1].

Fortunately, advances in the understanding of the pathophysiology of IHD have helped identify new pharmacological targets increasing the optimization of medical therapy. Of special interest, increasing evidence implicates altered cardiac energy metabolism at every stage of IHD, from stable angina to heart failure [2–5].

Although conventional drugs for stable angina indirectly address the basic problem of an imbalance between oxygen supply and demand, they do not act directly on energy metabolism in cardiomyocytes. This is addressed by the metabolic approach, which counteracts the deleterious consequences of ischemia by optimizing cardiac energy metabolism.

By specifically acting to improve cardiac energy metabolism, trimetazidine (TMZ) (Vastarel® MR) provides benefits complementary to those of classic hemodynamic therapy that, as a result, lead to greater clinical improvement across the wide range of ischemic heart diseases.

This article addresses the relevance of a cardiac energetic approach with TMZ MR in the treatment of stable IHD by highlighting its major clinical benefits in several subsets of high-risk patients, who are encountered more and more frequently in everyday practice, namely patients with diabetes, left ventricular (LV) dysfunction or revascularization, and the elderly.
Trimetazidine MR: an anti-ischemic treatment particularly suited to diabetic coronary patients

Diabetic patients have exacerbated metabolic disturbances of ischemia, increased vulnerability to ischemia and early decreased myocardial performance compared with non-diabetics, thus a therapeutic approach designed to improve cardiac energy metabolism is very well suited to these patients.

TMZ MR shifts cardiac energy metabolism from free fatty acid oxidation to glucose oxidation by selectively inhibiting the mitochondrial long-chain 3-ketoacyl coenzyme A thiolase (3 KAT), which catalyzes the terminal reaction of fatty acid beta-oxidation [6]. A shift toward glucose oxidation is likely to be beneficial during ischemia because adenosine-5‘-triphosphate (ATP) production per mole of oxygen consumed is about 12% higher when glucose is the energy substrate rather than fatty acids.

Also, by decreasing fatty acid oxidation and consequently re-activating the glucose pathway, TMZ MR prevents calcium overload and cell acidosis, and thus maintains cell homeostasis. In this way, ATP produced can mainly be used for contraction, so cardiac function is preserved.

Several studies in clinical practice have confirmed the major anti-ischemic and anti-anginal efficacy of TMZ MR in diabetic ischemic patients. In the DIETRIC study [7], which involved 580 diabetic patients with angina, a 6-month treatment with TMZ significantly reduced the incidence of angina episodes, improved results in the exercise tolerance test, and increased the time to ST-segment depression.

Moreover, a trial conducted with 24-hour ambulatory ECG monitoring showed that in diabetic coronary patients, treatment with TMZ significantly reduced the number of silent episodes of myocardial ischemia and the total duration of silent myocardial ischemia over 24 hours [8] (Fig. 1).

These results confirm the suitability of prescribing TMZMR to reduce not only symptomatic ischemic episodes, but also silent ischemia, a particularly important burden in diabetic ischemic patients.

In addition, TMZ MR has been shown in various trials to provide diabetic coronary patients with cardioprotective benefits by preserving their cardiac function, which is frequently impaired due to severe metabolic disturbances.

Fragasso et al. [9] studied the short- and long-term beneficial effects of TMZ in patients with diabetes and ischemic cardiomyopathy, and found that the drug consistently improved patients’ functional capacity and LV function. These benefits were recently confirmed in a randomized double-blind study by using gated single-photon emission computed tomography myocardial scintigraphy. The results showed that TMZ significantly improved the left ventricular ejection fraction (LVEF) (by 16%, p < 0.007 versus control group) and exercise tolerance (by 20.5%, p < 0.05 versus controls) of diabetic patients with ischemic cardiomyopathy.

These improvements were even more marked in patients with more severe reversible perfusion defects on initial evaluation [10].

Trimetazidine MR: clinical benefits in elderly ischemic heart disease patients

Elderly IHD patients have been shown to have a higher incidence of multivessel disease and silent ischemia than younger patients and often present a decrease in LV function. Furthermore, because of increased comorbidity and frequently atypical presentation of the disease, the diagnosis and management of elderly IHD patients is even more challenging. The clinical benefits of TMZ MR in elderly coronary patients have been confirmed in terms of efficacy, tolerability and improvement in quality of life.

The TRIMPOL I study confirmed the efficacy and acceptability of TMZ in a group of 71 elderly patients (age >65 years) with stable angina uncontrolled by other treatments [11]. The Trimetazidine in GERiatric patients (TIGER) multicenter study [12] in 141 angina patients aged 65 to 86 years showed similar results, with significant improvement in symptoms and exercise capacity in the TMZ treatment group. Finally, the study by Vitale et al. [13] showed the beneficial effect of TMZ in 47 elderly patients (average age, 78 years) with LV dysfunction and ischemic cardiomyopathy in comparison with placebo.

TMZ added to standard medical therapy significantly reduced angina attacks, and LVEF increased from 29% at baseline to 34.4% in the TMZ group, while no improvement was observed in the placebo group (p < 0.0001).
Moreover, a recent study by Marazzi et al. [14] assessed the effect of TMZ on the quality of life of elderly patients with ischemic cardiomyopathy. The overall assessment of quality of life using the visual analog scale showed a significant improvement in patients treated with TMZ (from 4.1 to 6.4, \( p < 0.01 \)), whereas no change was seen in patients receiving placebo.

In all these studies featuring frail patients, TMZ MR was well tolerated and safe. These additional attributes of TMZ MR ensure excellent compliance with treatment and contribute to the improvement in the quality of life of elderly patients.

**Trimetazidine MR: effective myocardial protection in revascularized patients**

Patients who have undergone myocardial revascularization constitute a growing proportion of patients with stable angina. TMZ MR has a documented antiischemic effect during myocardial revascularization procedures. Administration of TMZ MR prior to an intervention, whether percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), results in a reduction in plasma troponin release indicating a significant reduction in ischemic reperfusion injury of the heart.

Bonello et al. [15] reported the beneficial effects of pretreatment with an acute loading dose (60 mg) of TMZ before percutaneous transluminal coronary angioplasty (PTCA) in 266 patients with coronary artery disease (CAD). Prior to intervention, 136 patients were randomly assigned to the Vastarel group, and 130 to the control group. Troponin Ic (cTnI) levels were measured before and 6, 12, 18 and 24 hours after PTCA. Post-procedural cTnI levels were significantly reduced in the TMZMR–treated group at all time points (6 hours: \( 4.2 \pm 0.8 \) versus \( 1.7 \pm 0.2, p < 0.0001 \); 12 hours: \( 5.5 \pm 1.5 \) versus \( 2.3 \pm 0.4, p < 0.0001 \); 18 hours: \( 9 \pm 2.3 \) versus \( 3 \pm 0.5, p < 0.0001 \); and 24 hours: \( 3.2 \pm 1.2 \) versus \( 1 \pm 0.5, p < 0.0001 \)).

New data have come from Iskesen et al. [16], who investigated the protective effects of the preoperative use of TMZ MR on myocardial injury during open-heart surgery in a double-blind, parallel-controlled randomized study. Pretreatment with TMZMR in the treatment group began 2 weeks before the operation, while the control group did not receive this medication. The following biochemical markers were used to detect myocardial injury and therefore the degree of myocardial protection with TMZ MR: creatine kinase (CK), CK isoenzyme MB (CK-MB), troponin T, myoglobin and a lactate extraction calculation. The results show that post-operative levels of all these markers of myocardial injury were significantly lower in the Vastarel group than in the control group (\( p < 0.05 \)).

Lately, a 3-year study [17] has been investigating the early and long-term effects of TMZ MR in 306 patients with CAD undergoing CABG. Patients in the treatment group were randomly allocated to receive TMZ MR 2 weeks prior to CABG, which was continued for 3 years (\( n = 153 \)); the trial included a control group without TMZ MR (\( n = 153 \)).

In the early post-operative period, significantly lower plasma levels of creatine phosphokinase (CPK) and MB-CPK were found in the TMZ MR group (6 hours after CABG). Over the 3 years of follow-up, recurrence of angina was significantly lower in the TMZ MR group than in the control group (7.2% versus 12.4%, \( p < 0.05 \) (Fig. 2)).

Treatment with TMZ MR was also associated with a 15% increase in LVEF (\( p < 0.05 \)) versus no change in the control group (+1.5%, NS).

These results complement those from a subgroup analysis of the TRIMPOL II study. Ruzzyllo et al. [18] identified 94 patients with a history of revascularization for the treatment of CAD who were still symptomatic after 6 months in spite of treatment with metoprolol.

Compared with placebo, the 12-week treatment with TMZ MR significantly reduced the weekly number of angina attacks and nitrate consumption compared with placebo (\( p < 0.05 \)).

In all these studies conducted in patients undergoing revascularization, TMZ MR given prior to, during or after the intervention consistently had major antiischemic and cardioprotective effects.

**Trimetazidine MR: long-term cardioprotective benefits in patients with LV dysfunction**

The presence of systolic LV dysfunction is a key event in the course of IHD patients, worsening the prognosis and requiring adapted management. Unfortunately, in
many patients (50%–60% of cases) systolic LV dysfunction is asymptomatic and thus sometimes diagnosed when already severe and irreversible.

Data from the INDYCE survey, which evaluated systolic LV function prospectively in 3119 patients with stable IHD patients (68.4 ± 11.0 years; 80% men), show that the prevalence of LV dysfunction is quite high, with one patient in 3 presenting with moderate to severe LV dysfunction (LVEF < 50%) [19]. It is therefore necessary to consider the preservation of cardiac function when treating IHD patients.

The crucial role of myocardial energetic deficiency in LV dysfunction and the pathophysiology of heart failure, and the consequent rationale for treating this energy deficiency clinically by metabolic modulation has gained more and more recognition [2–5]. Moreover, numerous studies have highlighted the beneficial role of TMZ MR in IHD patients with LV dysfunction in various patient profiles, with different evaluation parameters and in short- and long-term follow-up.

Very recently, a publication in Heart grouped most of these studies into a large meta-analysis, which confirmed the beneficial effect of TMZ on top of standard therapy, in patients with LV dysfunction, mainly of ischemic origin [20]. This meta-analysis, which included 955 patients from 17 studies, shows that TMZ MR treatment is associated with a significant improvement across a wide range of contemporary, hemodynamic therapy, which lead to greater clinical complementary and synergistic to those of classic problem of an imbalance between oxygen supply and demand, while TMZ MR optimizes myocardial energy production by targeting cardiomyocytes directly.

That is why TMZ MR provides benefits that are complementary and synergistic to those of classic hemodynamic therapy, which lead to greater clinical improvement across a wide range of contemporary, high-risk subsets of patients, as a result. It is therefore a key player in the challenge of effectively managing the changing scenario of IHD.

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Focus on vastarel® MR
Clinical benefits of trimetazidine (Vastarel® MR) in the changing scenario of ischemic heart disease

Coronary microcirculation in effort ischemia: the roar of the rabbit

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Abstract

A 71-year-old man was admitted to our department with a history of effort angina, positive exercise stress test, and single photon emission computed tomography (SPECT) results indicative of reversible ischemia in the left anterior descending artery (LAD) territory. Coronary angiography showed no significant atherosclerotic lesions in either right or left coronary arteries. However, a relevant slow flow in the LAD artery was detected. In a traditional interpretation, the SPECT results would be seen as a false positive for coronary artery disease. In our opinion, the case is instead a true positive for coronary microvascular dysfunction. The pathophysiology of myocardial ischemia is not confined to the epicardial coronary level but globally involves coronary arteries, microcirculation, and myocardium.

Keywords: Coronary angiography, coronary slow flow, myocardial ischemia

History

A 71-year-old man was admitted to our department with a history of effort angina and a diagnosis of inducible ischemia. As coronary risk factors, he had essential hypertension and dyslipidemia.

In 2008, because of effort angina, he performed a treadmill exercise test that showed a significant ST-segment depression in V4-V6 leads, so he also underwent an exercise single photon emission computed tomography (SPECT). The examination detected a reversible perfusion defect in the inferior septum with a normal left ventricular ejection fraction (LVEF). Coronary angiography showed a 50% diameter stenosis in the mid left anterior descending coronary artery (LAD); this lesion was not treated with angioplasty because the fractional flow reserve (FFR) resulted in the normal range (0.87).

In October 2010, a few weeks before admission, the patient underwent a second exercise test for the persistence of effort angina despite medical treatment; the test was positive for inducible ischemia. He also repeated an exercise SPECT: the electrocardiogram (ECG) showed a downsloping ST-segment depression (2 mm) in V5-V6 leads (Figure 1), while the perfusion scan documented a moderate and reversible defect in the mid septum (Figure 2).

When the patient was admitted, he had a normal sinus rhythm. Echocardiography showed normal left ventricular volumes, wall thickness and LVEF (58%), without wall-motion abnormalities. Due to his high Framingham Risk Score and the positive SPECT results, we decided to perform a second coronary angiography. Coronary arteriography showed the absence of lesions in the right coronary and circumflex arteries and a non-critical stenosis (<50% luminal diameter narrowing) in the mid-LAD (Figure 3). The most important finding was the delayed progression of the contrast agent in the whole LAD artery that resulted in a Thrombolysis In Myocardial Infarction (TIMI) 2 flow (45 frames to opacify the distal vasculature, against 5 beats for the right coronary and circumflex artery). The corrected TIMI frame count for LAD (CTFC) was 26 [1]. The left ventriculography confirmed the absence of wall-motion abnormalities and a good LVEF (56%).

Case report
Discussion

We present a case report of ischemic heart disease (IHD) in the absence of epicardial coronary artery stenoses. Nearly 50 years after the introduction of coronary angiography, the anatomical approach to ischemic heart disease, directed to the coronary stenosis, remains the most popular way to manage such disease.

However, we know that atherosclerosis, traditionally considered a focal cholesterol storage disease, is instead a widespread inflammatory process, responsible for the development, evolution and complications of arterial lesions [2,3]. Furthermore, it is

Case report

Coronary microcirculation in effort ischemia: the roar of the rabbit

Figure 1. The exercise test results positive (arrows) in V5V6 leads at 100 Watts.

Figure 2. The SPECT images revealed a reversible defect in the mid septum.

Figure 3. The corrected Thrombolysis In Myocardial Infarction (TIMI) frame count (CTFC) introduced by Gibson is a quantitative and reproducible index of coronary artery flow. It represents the number of cine frames required for contrast to reach a pre-specified distal coronary artery landmark. Coronary slow flow phenomenon is defined as CTFC greater than 2 standard deviations (SD) from the normal published range, which is 21 ± 3.5. Point A is the frame count when the ostium of the vessel gets opacified. Point B is the frame count when the pre-specified most distal vessel segment gets opacified. CTFC = 45/1.7 = 26 (1.7 is the correction factor) used for the left anterior descending artery (LAD) due to its longer length.
now recognized that most atherosclerotic lesions grow outward, so a consistent burden of atherosclerosis can exist in the absence of stenoses. Finally, in the setting of acute coronary syndromes (ACS), Riofol et al demonstrated that vulnerable plaques are present throughout the coronary tree, regardless of the culprit lesion [4].

In reality, the pathophysiology of ischemic heart disease is not confined to epicardial coronary stenosis, but is much more complicated and invariably involves both coronary microcirculation and the myocardium.

Several published series have demonstrated that a large number of patients with symptoms and signs of ischemic heart disease have no stenoses at coronary angiography. In the setting of ACS, the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO) IIb trial demonstrated in a large cohort that about 30% of patients had no culprit lesions [5]. The same result was recently confirmed by the Coronary Artery Spasm in Patients With Acute Coronary Syndrome (CASPER) study, which also documented that epicardial coronary vasospasm was responsible of the ACS in the half of the cases [6].

As regards stable angina, the Coronary Artery Surgery Study (CASS), involving 21,487 angiograms, showed that 18.8% of patients had non-obstructive coronary artery disease [7] and, among women, this percentage raises up to 50%, as documented by the Women’s Ischemia Syndrome Evaluation (WISE) study [8].

Likoff et al [9] and Kemp [10] reported two studies in which patients with ST-segment depression or T-wave inversion at rest accentuated such ECG changes during exercise despite normal coronary angiography. Abnormalities in coronary flow and metabolic responses to stress were reported over the years by several groups, all findings consistent with a microvascular etiology for ischemia and symptoms [11,12], the so-called microvascular angina.

The coronary slow-flow phenomenon (CSFP), documented in our case report, is defined as an abnormal condition in which (micro)vascular resistances are inappropriately high, causing a slow anterograde progression of the contrast medium [13]. CSFP was widely recognized as a marker of myocardial ischemia [14]. The overall incidence of CSFP has been reported as 1% among patients undergoing coronary angiography, especially in patients presenting with acute coronary syndromes [15]. In the TIMI-IIIa study, the incidence of CSFP was approximately 4% among patients presenting with unstable angina and without significant epicardial coronary artery disease [16]. Myocardial perfusion scintigraphy shows reversible perfusion abnormalities in 28–75% of patients with CSFP [17,18].

Different theories have been postulated about the cause of small-vessel dysfunction, including microvascular tone alteration, small-vessel wall thickening [19], patchy fibrosis [20], and impaired endothelial release of nitric oxide (NO) [21]. In any case, structural or functional alterations of coronary microcirculation have been documented in several clinical conditions, such as stable and unstable angina [22–27]. In these conditions, endothelial and microvascular dysfunction play a pathophysiological role both in the precipitation and maintenance of myocardial ischemia, also in the absence of coronary atherosclerosis.

The discussion of our case report should focus on two main questions. The first issue is whether or not our patient suffered from IHD despite the absence of coronary artery disease (CAD). The second is the significance of a positive stress test in absence of CAD.

The answer to the first question is undoubtedly yes. Our patient had not only a long history of stable, reproducible, and typical angina on effort but also unequivocal signs of myocardial ischemia documented by both electrocardiographic and myocardial perfusion markers. The patient had moderate perfusion defects on stress imaging SPECT. We know that, regardless of the diagnostic approach, 5% or more of ischemic myocardium is an important measure of 2-year risk of death or MI [28].

Regarding the second issue, many stress tests have been evaluated to clarify their diagnostic and predictive accuracy [29,30]. In our case, the SPECT result would be conventionally rated as a false positive result for CAD, even in the presence of typical symptoms and other unequivocal signs of inducible ischemia. In reality, our case report demonstrates that exercise stress test and SPECT results must be regarded as a true positive result for coronary microcirculatory dysfunction and microvascular ischemia. Patel et al [31], in a recently published paper, show that, although a positive test is highly predictive of coronary obstructions, significant coronary stenoses are present in >30% of patients with negative exercise test, both symptomatic and asymptomatic. Therefore, CAD does not necessarily imply IHD, since ischemic syndromes often manifest in absence of coronary atherosclerosis and, vice versa, even a severe coronary atherosclerosis frequently occurs in the absence of documentable ischemia.

**Conclusion**

IHD is a multi-factorial syndrome, with a complex pathophysiology that goes far beyond coronary stenosis and involves both coronary microcirculation and the myocardium.
References

Lessons from EUROASPIRE I, II, and III surveys

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Abstract

The European Society of Cardiology (ESC) has carried out three surveys with the acronym EUROASPIRE (European Action on Secondary and Primary Prevention through Intervention to Reduce Events) on lifestyle and risk-factor management and use of drug therapies in patients with coronary heart disease (CHD), and in asymptomatic individuals at high risk of developing cardiovascular disease (CVD) in Europe. EUROASPIRE I was conducted during 1995–1996 in nine countries, EUROASPIRE II during 1999–2000 in 15 countries, and EUROASPIRE III during 2006–2007 in 22 countries. The EUROASPIRE III survey was extended beyond coronary patients to include apparently healthy individuals being treated as at high cardiovascular risk due to markedly raised blood pressure, total cholesterol, or diabetes in general practice in 12 European countries.

The results of the European surveys show that the lifestyle of coronary and high-risk patients is a major cause of concern, with persistent smoking and high prevalence of both obesity and central obesity. Blood pressure, lipids and glucose control are inadequate, with most patients, not achieving the targets defined in the prevention guidelines. There is considerable potential throughout Europe to raise the standard of preventive cardiology through more lifestyle intervention, control of other risk factors, and optimal use of prophylactic drug therapies. Cardiovascular disease prevention needs a comprehensive, multidisciplinary approach that addresses lifestyle and risk-factor management by cardiologists, general practitioners, nurses and other health professionals, and a healthcare system that invests in prevention.

Keywords: Cardiovascular disease (CVD), coronary heart disease (CHD), EUROASPIRE, lifestyle and risk-factor management

Introduction

Cardiovascular disease (CVD) is the major cause of death, hospital admissions and disability in middle-aged and older patients in Europe [1,2]. The main objectives of CVD prevention are to reduce the risk of first or recurrent atherosclerotic events and to improve both quality of life and life expectancy for people at increased risk of developing CVD and those with established cardiovascular disease. The Joint European Societies (JES) guidelines on prevention of CVD in clinical practice published in 1994, 1998, 2003 and 2007 made recommendations for a healthier lifestyle and set goals for blood pressure, lipid and glucose management and the use of cardioprotective medication [3–6].

However, risk-factor management in patients with coronary heart disease (CHD) and those at high risk of developing CVD in Europe is far from optimal. Guidelines implementation in daily clinical practice has been evaluated with three cross-sectional surveys called EUROASPIRE (European Action on Secondary and Primary Prevention through Intervention to Reduce Events) starting in mid-1990s. The European

EUROASPIRE surveys

The first EUROASPIRE survey was carried out in coronary patients in nine European countries: Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, Slovenia, and Spain [7]. Following the publication of the 1998 JES recommendations on coronary prevention, the second EUROASPIRE survey was conducted in 15 European countries: Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Poland, Slovenia, Sweden, Spain, and the United Kingdom [8,9]. The results of the EUROASPIRE I and II surveys demonstrated a high prevalence of modifiable risk factors in patients with CHD and wide variations in medical practice between countries. The third EUROASPIRE survey was extended beyond coronary patients to include apparently healthy individuals at high risk of developing CVD. In this way the EUROASPIRE III survey covered the complete spectrum of patient priorities as defined in the guidelines [10–12].

The EUROASPIRE III survey was carried out in selected geographical areas in 22 countries in Europe (Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, the Netherlands, Poland, Romania, Russian Federation, Slovenia, Spain, Turkey, and the UK) [10].

The overall objectives of EUROASPIRE III survey were:

1. To determine whether the Joint European Guidelines on cardiovascular disease prevention are being followed in hospitalized coronary patients (acute myocardial infarction and ischemia and following revascularization by angioplasty or coronary artery surgery) and in high CVD-risk individuals being treated in primary care.
2. To determine whether the practice of preventive cardiology in patients with established coronary disease in EUROASPIRE III had improved by comparison with those centers that took part in EUROASPIRE I and II.

The main outcome measures were the proportions of coronary and high cardiovascular risk patients achieving the lifestyle, risk factor and therapeutic targets for cardiovascular disease prevention.

In the hospital arm, consecutive patients—men and women <80 years of age, with a clinical diagnosis of CHD (coronary artery bypass graft operation [CABG], percutaneous coronary intervention [PCI], myocardial infarction [MI] or acute myocardial ischemia without MI)—were identified retrospectively from medical notes and interviewed and examined at least six months after their acute coronary event or procedure.

A total of 13,935 medical records were reviewed and 8,966 patients (25.3% women) interviewed on average 1.24 years following their index event (participation rate 73.0%). At interview, 17.2% of patients smoked cigarettes, 81.8% had body mass index (BMI) >25 kg/m², 35.3% were obese (BMI >30 kg/m²), 52.7% had central obesity (waist circumference >102 cm in men or >88 cm in women), and 56.0% had raised blood pressure (BP >140/90 mmHg; >130/80 mmHg for patients with diabetes). The prevalence of elevated total cholesterol (>4.5 mmol/l) and LDL-cholesterol (>2.5 mmol/l) was 51.1% and 54.5% respectively; 36.7% had decreased serum HDL cholesterol (<1 mmol/l for men and <1.2 mmol/l for women) and 34.7% had triglycerides >1.7 mmol/l. In addition, 34.8% had diabetes (self reported or fasting plasma glucose >7 mmol/l). The therapeutic control of blood pressure (BP) was poor, with only 37.3% of patients on blood pressure lowering medication being controlled (BP <140/90 mmHg; <130/80 mmHg for patients with diabetes). In those on lipid-lowering medication, just over a half (55.0%) had reached the total cholesterol goal of <4.5 mmol/l. Only 10.4% of patients with self-reported diabetes had fasting plasma glucose <6.1 mmol/l and 34.7% had HbA1c <6.5%. The use of cardioprotective medication was as follows: aspirin or other anti-platelets drugs, 90.5%; beta-blockers, 79.8%; angiotensin-converting enzyme (ACE) inhibitors, 59.9%; angiotensin-receptor blockers (ARBs), 12.0%; statins, 78.1%; and anticoagulants, 5.6%.

The comparison between those eight countries that participated in the EUROASPIRE I, II and III surveys demonstrates a compelling need for more effective lifestyle management of coronary patients [11]. Adverse trends in smoking prevalence in younger women and the alarming increase in obesity, central obesity and diabetes are an increasing cause for concern. The overall prevalence of smoking was virtually unchanged (20.3%, 21.2%, and 18.2% respectively) but had increased in younger (<50 years) women from 30.0% to 50.0% over this period. The prevalence of obesity increased substantially: 25.0%, 32.6%, and 38.0% respectively, with a corresponding increase in central obesity. Despite a substantial increase in the use of anti-hypertensive medications, blood pressure management remained unchanged, and although lipid management continues to improve, because of statin therapy, almost half of all patients were still above the recommended lipid targets. The proportion of patients with a raised blood pressure (>140/90 mm Hg for non-diabetics and >130/80 in patients with diabetes) was virtually unchanged-58.1%, 58.3% and 60.9% with nearly three-fifths of all patients on blood
pressure lowering medication not achieving the blood pressure goal in the third survey. The prevalence of elevated total cholesterol (>4.5 mmol/l) had decreased substantially: 94.5%, 76.7%, and 46.2%. However, nearly two-fifths of patients on lipid-lowering medication in the third survey had not reached the total cholesterol goal. The prevalence of self-reported diabetes mellitus increased across the surveys — 17.4%, 20.1%, and 28.0% respectively. Cardioprotective drug use had also increased across the surveys: aspirin or platelet-active drugs 80.8%, 83.6%, and 93.2%; beta-blockers 56.0%, 69.0%, and 85.5%; ACE inhibitors/ARBs 31.0%, 49.2%, and 74.2%; and lipid-lowering drugs 32.2%, 62.7%, and 88.8%.

The general practice arm was carried out in 12 European countries: Belgium, Bulgaria, Croatia, Finland, Germany, Italy, Latvia, Poland, Romania, Slovenia, Spain, and the United Kingdom [12]. Consecutive patients, men and women <80 years of age, without a history of coronary or other atherosclerotic disease, either started on antihypertensive and/or lipid lowering and/or anti-diabetes treatments, were identified retrospectively and interviewed and examined at least six months after the start of medication.

A total of 5,687 medical notes were reviewed and 4,366 patients (57.7% females) considered to be at high cardiovascular risk were interviewed after the start of drug treatment (participation rate 76.7%). Overall, 16.9% smoked cigarettes, 43.5% were obese (BMI >30 kg/m²) and 61.6% centrally obese (waist circumference >102 cm in men or >88 cm in women), 70.8% had blood pressure >140/90 mm Hg (>130/80 in people with diabetes mellitus), 66.4% had total cholesterol >5 mmol/l (>4.5 mmol/l in people in diabetes), and 38.6% had diabetes (self-reported or fasting plasma glucose >7 mmol/l). The risk factor control was very poor, with only 26.3% of patients using anti-hypertensive medication achieving the blood pressure goal, and 30.6% of patients on lipid-lowering medication achieving the total cholesterol goal. Only 8.6% of patients with self-reported diabetes had fasting plasma glucose <6.1 mmol/l and 39.9% had HbA1c <6.1%. The use of blood pressure lowering medication in people with hypertension was: beta-blockers, 34.1%; ACE inhibitors/ARBs, 60.8%; calcium channel blockers, 26.3%; diuretics, 36.9%. Statins were prescribed in 47.0% of people with hypercholesterolemia. Of all patients, 22.0% were on aspirin or other anti-platelet medication.

The European challenge for preventive cardiology

The EUROASPIRE surveys give a unique European picture of preventive cardiology as practiced by cardiologists, other specialists and primary care physicians looking after patients with coronary disease and their families, and also people at high risk of developing CVD. They provide an objective assessment of clinical outcomes at least a year after their index event, either for hospitalization with coronary disease or having been started on medical therapy in primary care. The results show that the lifestyle of coronary and high-risk patients is a major cause for concern, with persistent smoking, especially among younger patients and high prevalence of both obesity and central obesity. Blood pressure, lipid and glucose control are inadequate, with most patients not achieving the targets defined in the prevention guidelines. There is considerable potential throughout Europe to raise the standard of preventive cardiology care through more effective lifestyle intervention, rigorous control of other risk factors, and optimal use of prophylactic drug therapies. It is possible to further reduce the gap between guideline standards and clinical practice by providing a comprehensive program of preventive care addressing all aspects of lifestyle and risk factor management by cardiologists, general practitioners, nurses and other allied health professionals, and a healthcare system that invests in prevention.

Acknowledgements

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References


Interventional therapy for resistant hypertension: new hopes and old concerns!

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Hypertension contributes to 62% of all strokes and 49% of all cases of heart disease and is the most prevalent controllable disease in developed countries, affecting 20–50% of adult population [1]. Nevertheless, it has been estimated that only 5–30% of patients with hypertension achieve adequate blood pressure control [2], with challenges to obtain target values mainly ascribed to insufficient diagnosis, ineffective treatment, or low patient adherence to lifelong medical therapy. However, even when these difficulties are overcome and patients are on three or more antihypertensive drugs, about 20–30% will still continue to present with high pressure values, a condition known as “resistant hypertension.” Given these unsatisfactory results [3], the rationale for establishing alternative treatment options, rather than just appropriate ones, appears legitimate. Renal sympathetic denervation by means of percutaneous, catheter-based ablation technique is a novel emerging therapeutic strategy, currently under clinical evaluation.

Rationale for targeting renal sympathetic nervous system

Hemodynamic load, neurohumoral modulators, and renal sympathetic activity control the regulatory actions of the kidneys. Chronic activation of the latter is considered a maladaptive response and has been attributed an important role in the initiation, development, and maintenance of hypertension [4]. Two main mechanisms have been proposed as triggering events for chronically elevated sympathetic nervous activity (SNA): 1) primarily elevated afferent SNA [8] and 2) intrarenal pathology, such as ischemia, hypoxia, or other injury, that results in an increase in renal afferent activity [5–7]. Increased SNA and renal injury in the genesis of hypertension are still considered a sort of “chicken and egg” dilemma. However, regardless of the triggering mechanism, the crucial role of SNA in the maintenance of hypertension has been confirmed both in animal models [9–11] and patients with essential hypertension. These hypertensive models present with an increased efferent renal sympathetic nerve activity [12–14], which has been shown to be under direct control of renal sensory afferent nerve activity that acts through modulation of the posterior hypothalamic activity [15]. This complex interaction translates into an increased renin release [16], increased sodium reabsorption [17], and a reduction of renal blood flow [18–23], thereby turning out into an auto-maintained vicious circle.

An overall increased SNA has also been shown in heart failure patients [24] where increased concentrations of plasma norepinephrine (NE) are associated with a strong negative predictive value on all-cause mortality in an independent way from either glomerular filtration rate or left ventricular ejection fraction [25]. Accordingly, in animal models, renal sympathetic denervation (RSD) of heart failure- and obesity-related hypertension resulted in reduced morbidity and mortality [26,27]. Consequently, while initially used as a physiological tool to elucidate the role of sympathetic activity in pathological states such as hypertension, heart failure, etc., RSD ended up revealing a potential therapeutic strategy [21]. In addition, further support that the denervated kidney reliably sustained electrolyte and volume homeostasis and that nephrectomy of the native kidney resulted in the reduction of systemic vascular resistance became available from human transplant experience [28].

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Evolution of the RSD therapeutic approach

Surgical denervation for blood pressure control is an old concept and was attempted, although unsuccessfully, since early 1950s. Subdiaphragmatic splanchnicectomy in severely hypertensive patients resulted in high perioperative morbidity and mortality, as well as long-term complications, such as bowel and erectile dysfunction and profound postural hypotension [29,30]. These deleterious side effects were principally ascribed to surgical techniques used in the past that did not specifically target the renal nerves. Similarly, given the impossibility of regional action, pharmacologic assault on sympathetic nerve function was also associated with systemic complications. In contrast, more selective animal models of denervation, targeting renal SNA with either surgical stripping or selective infusion of drugs proved to be safer and more effective [31]. Renal sympathetic nerves are derived from numerous spinal ganglia, and arborize throughout the adventitia of the renal artery, therefore representing a difficult surgical target. The first attempt of selective renal nerve ablation with radiofrequency catheter in hypertensive swine resulted in a markedly reduced content of NE (>85%), which was very similar to the effects of direct surgical renal denervation. An important goal for clinical scientists is translation of pathophysiological knowledge into better treatment strategies for patients. Shortly after, transcatheter radio-frequency ablation was in fact adopted into clinical practice with a safety and proof-of-concept human trial [32] and other case reports [33]. In November 2010 the first randomized controlled trial was presented at the American Heart Association Scientific Sessions [34]. In this study, patients were randomized either to traditional medical therapy or traditional medical therapy plus catheter-based radiofrequency ablation. In this approach a catheter is placed in both renal arteries one at a time and circular burns using radio waves are performed in different areas to prevent the formation of a narrowing or an aneurysm in the arteries. There was a significant decrease in blood pressure levels in the treatment group, which was confirmed at six-month follow-up. No serious procedure-related or device-related complications were reported and occurrence of adverse events did not differ between groups.

Unmet needs and clinical prospective

Catheter-based RSD therapy affirms the crucial relevance of renal nerves in the maintenance of elevated blood pressure (BP) levels. While once-and-for-ever treatment represents the ultimate goal, the first natural step after successful renal denervation is a reduction in antihypertensive medicines necessary to control BP values of hypertensive patients. However, some features of the available data deserve further considerations. Not all patients undergoing catheter-based ablation achieve BP “control,” defined as systolic BP of <140 mm Hg. Of the patients achieving BP control, only a minor fraction are able to reduce the number of drugs they were taking or the dose of those drugs. Moreover, a consistent number of patients undergoing percutaneous RSD experience only a minimal BP drop and are, therefore, considered “nonresponders.”

Finally, concerns related to this new therapeutic approach also appear legitimate. Given the invasive nature of the technique, do these results justify procedural related risks of RSD? How do we interpret the partial benefits in this patient population? Are there any clinical predictors for response? Will catheter-based RSD be an additional arsenal in our therapeutic armamentarium, or just another shooting star?

Theoretically the partial benefits can be explained by two main mechanisms: either the denervation was not successful or nerve traffic to the kidney may not be the only mechanism responsible for “re-resistant” hypertension.

The efficacy of renal denervation can be established by isotope dilution-derived measurement of organ-specific NE release to plasma (regional “NE spillover”). Although catheter-based RSD resulted in a significant mean fall in NE spillover, denervation was proven to be not complete in radiofrequency ablation group [32]. Technical issues in this upcoming interventional area will represent an additional challenge for the amateur cardiologists. However, incomplete RSD does not fully justify the partial benefits for BP control achieved in these studies. The old assumption was that the sympathetic nervous system acted in a global and undifferentiated fashion. However, overall sympathetic nervous system activity is often regionalized in domains such as heart, kidneys and vascular barore-flex system, and may present a varying degree of relative activation and therefore clinical relevance [24–27,35–39]. In line with these considerations, another interventional therapeutic strategy with surgically implantable arterial barostimulator has been proven to be effective in resistant hypertension patients [40,41]. This bilateral implantable device operates by continuous electrical stimulation of the carotid sinus buffer nerves and culminates in reduced circulating NE levels. This effect translates in reduced BP values, hence underscoring the role of a sympathetic, although nonrenal, BP control mechanism [42].

In conclusion, recently published clinical trials have shown very interesting and promising data on radiofrequency, catheter-based, percutaneous RSD. Nevertheless, as traditionally in the history of medicine, a given therapy may not always equally benefit patients with apparently similar pathophysiological...
conditions. Whether optimal results are lacking because of technical issues or an incomplete understanding of the role of SNA in essential hypertension remains still to be determined. Therefore, converging efforts from both interventional cardiologists and clinical researchers to improve the potentials of this treatment strategy will be decisive in promoting percutaneous RSD as an established therapeutic option in the near future.

References

Gadolinium

Gadolinium is a rare-earth metal that can be used as a research tool for applications such as magnetic resonance imaging (MRI). It can be used as MRI contrast agent, since as a paramagnetic ion it moves differently within a magnetic field. Gadolinium can also be used in ion channel electrophysiology experiments to block sodium channel leaks, as well as to stretch activated ion channels.

Renin

Renin is an enzyme that participates in the body’s renin-angiotensin system (RAS) and mediates blood volume and arterial vasoconstriction. It is therefore an important regulator of blood pressure. Renin is secreted by the kidney granular cells of the juxtaglomerular apparatus and hydrolyzes angiotensinogen secreted from the liver into the peptide angiotensin I. Angiotensin I is then converted by endothelial-bound angiotensin converting enzyme (ACE) into angiotensin II, a potent constrictor of blood vessels.

Norepinephrine

Norepinephrine (sometimes called noradrenaline) is a catecholamine with multiple roles, including as a hormone and a neurotransmitter. Along with epinephrine (adrenaline), norepinephrine is also part of the fight-or-flight response, and directly increases heart rate, triggers the release of glucose from energy stores, and increases blood flow to skeletal muscle. Norepinephrine also increases blood pressure by increasing vascular tone through α-adrenergic receptor activation. The actions of norepinephrine are carried out via binding to adrenergic receptors.

Sodium excretion

Sodium is filtered by the kidney and can be excreted in the urine. Sodium excretion is measured in terms of plasma and urine sodium, rather than by the interpretation of urinary sodium concentration alone, as urinary sodium concentrations can vary with water resorption. Therefore the urinary excretion rate can be used to get a measure of renal clearance. Sodium excretion is used in acute renal failure in order to determine if hypovolemia or decreased effective circulating plasma volume is a contributor to renal failure.

Troponins

Troponins are important proteins involved in muscle contraction. They are located within grooves between actin filaments in muscle tissue. Troponins consist of three subunits: troponin C (TnC), troponin I (TnI), and troponin T (TnT). Binding of calcium to TnC results in a shift in tropomyosin such that actin filaments can interact with myosin to produce force and/or movement. In the absence of calcium, tropomyosin interferes with this action of myosin, and therefore muscles remain relaxed. TnT binds to tropomyosin, interlocking them to form atronopin-tropomyosin complex. TnI binds to actin in thin myofilaments to hold the tropo- nin-tropomyosin complex in place.