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REVIEW

Physiology of *in-situ* arterial revascularization in coronary artery bypass grafting: Preoperative, intraoperative and postoperative factors and influences

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Abstract

Surgical revascularization with coronary artery bypass grafting (CABG) has become established as the most effective interventional therapy for patients with moderately severe and severe stable ischemic heart disease (SIHD). This recommendation is based on traditional 5-year outcomes of mortality and avoidance of myocardial infarction leading to reintervention and/or cardiac death. However, these results are confounded in that they challenge the traditional CABG surgical tenets of completeness of anatomic revascularization, the impact of arterial revascularization on late survival, and the lesser impact of secondary prevention following CABG on late outcomes. Moreover, the emergence of physiologic-based revascularization with percutaneous cardiovascular intervention as an alternative strategy for revascularization in SIHD raises the question of whether there are similar physiologic effects in CABG. Finally, the ongoing ISCHEMIA trial is specifically addressing the importance of the physiology of moderate or severe ischemia in optimizing therapeutic interventions in SIHD. So it is time to address the role that physiology plays in surgical revascularization. The long-standing anatomic framework for surgical revascularization is no longer sufficient to explain the mechanisms for short-term and long-term outcomes in CABG. Novel intraoperative imaging technologies have generated important new data on the physiologic blood flow and myocardial perfusion responses to revascularization on an individual graft and global basis. Long-standing assumptions about technical issues such as competitive flow are brought into question by real-time visualization of the physiology of revascularization. Our underestimation of the impact of Guideline Directed Medical Therapy, or Optimal Medical Therapy, on the physiology of preoperative SIHD, and the full impact of secondary prevention on post-intervention SIHD, must be better understood. In this review, these issues are addressed through the perspective of multi-arterial revascularization in CABG, which is emerging (after 30 years) as the "standard of care" for CABG. In fact, it is the physiology of these arterial grafts that is the mechanism for their impact

on long-term outcomes in CABG. Moreover, a better understanding of all of these preoperative, intraoperative and postoperative components of the physiology of revascularization that will generate the next, more granular body of knowledge about CABG, and enable surgeons to design and execute a better surgical revascularization procedure for patients in the future.

Key words: Coronary artery bypass grafting; Arterial revascularization; Myocardial perfusion; Surgical outcomes; Intraoperative imaging

Core tip: This review examines the emerging understanding of physiology in revascularization from the preoperative, intraoperative and postoperative perspectives. The particular importance of physiology in arterial revascularization, which is becoming the standard of care, is discussed using novel intraoperative imaging data results. These imaging data objectively confirm certain physiologically-determined outcomes, and highlight inadequacies in a number of long-standing assumptions about surgical revascularization with coronary artery bypass grafting.

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INTRODUCTION

Arterial revascularization, and in particular complete arterial revascularization, is a current emerging trend in surgical revascularization with coronary artery bypass grafting (CABG). This Review examines the physiologic aspects of arterial revascularization in light of its documented clinical outcomes benefits (Table 1).

ARTERIAL REVASCULARIZATION IN CABG

Since its inception in the 1960s, the history of CABG has included incremental developments to improve outcomes[1]. Among these, the use of *in situ* internal mammary artery (IMA) grafting has been documented to have the most profound beneficial effect[2,3]. Placed to the left anterior descending coronary artery (LAD), this intervention is perhaps the most singularly effective in all of ischemic heart disease[4,5]. Multiple studies have documented excellent short-term angiographic results, superior long-term patency *vs* other conduits, and a direct impact on long-term survival in observational studies[6,7]. Interestingly, this benefit appears to have its maximal impact 10-20 years post-surgery, after most non-arterial conduits have lost their efficacy[8].

Surgical groups with a long-standing interest in multi-arterial grafting have hypothesized about the mechanism(s) for this incremental benefit on survival, based on their excellent observational studies[9-11]. With improvement in techniques such as skeletonization[12], the use of bilateral arterial grafting is being advocated as the new "standard" of care[13,14]. This despite the additional work product and time required for this surgical approach, because of it's association with significantly better long-term outcomes[15].

The standard explanation for these improved outcomes is the substantial long-term anatomic patency of arterial grafts, both early and late[16]. While this certainly is a factor, the complete mechanism is more complicated. Indeed, as our understanding of the physiologic substrates for stable ischemic heart disease (SIHD) and acute coronary syndrome (ACS) have evolved, it is clear that physiologic factors are as if not more important than anatomic factors, which have for years formed the based of technical surgical revascularization design and execution.

Thus the premise of this review is that the true impact of multi-arterial *in situ* grafting in CABG results from its impact on the physiology of myocardial revascularization in that patient.

PREOPERATIVE FACTORS AND INFLUENCES

The revascularization strategy that is CABG today should be very different from previous iterations, in order to take advantage of: (1) concomitant developments in ischemic heart disease therapies and their physiologic impact on SIHD and ACS; and (2) the changes in the patient population of those patients coming to surgery, and the changes in the myocardial pathophysiologic substrate in these new patients. Truly innovative improvements in surgical revascularization must address these physiologic and pathophysiologic substrate issues in order to be successful.

Nowhere has this been more evident than in the emergence of optimal medical therapy (OMT), or guideline-directed medical therapy (GDMT), in SIHD[17]. From an afterthought 10-15 years ago, GDMT has emerged as an initial mainstay of therapy for SIHD patients outside the scope of ACS, where emergent intervention can be life-saving[18]. The impact of GDMT on clinical survival outcomes was documented in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and trial substudies in patients with mild to moderate ischemia[19-22]. These findings are not without controversy, however[23,24], with particular attention to their impact on early inter-

Table 1 Factors and influences in arterial revascularization

Arterial revascularization in CABG
Emerging "standard of care" for CABG
Years of data to document benefits, but slow to adopt
Both based on long term survival outcomes
Mechanisms for increased survival based on traditional anatomic construct for surgical revascularization
Better long-term graft patency
Preoperative factors and influences
Effectiveness of GDMT - physiologic modulation of underlying ischemia
Extent of disease
Collateral development
Influence on myocardium
Impact on subsequent revascularization
ISCHEMIA trial
Equipoise issue
Implications for revascularization
Same physiologic principles impacting PCI must also impact CABG
Difference in anatomic extent of disease
Surgical revascularization not dependent on completeness of (anatomic) revascularization
Intraoperative factors and influences
Dynamic nature of *in situ* arterial grafts
Competitive flow in arterial grafts (*vs* vein grafts)
Incomplete revascularization *vs* appropriate incomplete revascularization
FFR-based revascularization
Postoperative factors and influences
Secondary prevention measures in CAD
DAPT
Secondary prevention efforts following CABG

CABG: Coronary artery bypass grafting; GDMT: Guideline directed medical therapy; PCI: Percutaneous cardiovascular intervention; DAPT: Dual anti-platelet therapy; FFR: Fractional flow reserve; ISCHEMIA: International Study of Comparative Health Effectiveness with Medical and Invasive Approaches.

vention revascularization strategies, mostly for percutaneous coronary intervention (PCI) but also for CABG[17]. The COURAGE population had predominantly mild ischemia symptoms and objective findings, and early PCI in these patients demonstrated no benefit in terms of the primary outcome of death from any cause and non-fatal myocardial infarction (MI)[19].

The importance of preoperative ASA, beta-blockers and statins on CABG surgical outcomes have all been examined as well. Preoperative beta-blockade was documented to positively impact on CABG outcomes in 2002[25], with incorporation into the National Quality Forum Quality Measures for CABG Surgery and the ACCF/AHA Guidelines for CABG[26]. A decade later, this benefit was re-examined in a more contemporary patient population, and no longer found to be a statistically significant influence on survival[27]. Rather than indicating the loss of effectiveness of beta-blocker therapy in CABG patients however, or that the initial studies were flawed, these findings almost certainly reflect the change in the underlying physiologic substrate of patients coming for contemporary CABG[28,29].

In patients with SIHD, GDMT is necessary because it prevents MI and death. The mechanism for the effectiveness of GDMT is the beneficial modulation of the underlying physiologic substrates of hypoperfusion/ischemia, atherosclerosis, myocardial contractility and relaxation, and microvascular and macrovascular myocardial blood flow[30]. Obviously, these same factors greatly influence CABG patients as well.

The impact of GDMT with and without early revascularization in patients with moderate to severe ischemia is currently being tested in the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, (NCT01471522). The aim of the ISCHEMIA trial is to determine whether an initial invasive strategy of cardiac catheterization and optimal revascularization (with PCI or CABG, as determined by the local heart team) plus OMT will reduce the primary composite endpoint of cardiovascular death or nonfatal MI in SIHD with moderate or severe ischemia and medically controllable or absent symptoms, as compared with an initial conservative strategy of OMT alone, with catheterization reserved for failure of OMT (Figure 1). The major secondary endpoint is angina-related QoL. Other important secondary endpoints are health resource utilization, costs and cost effectiveness. The ISCHEMIA study thus aims to address limitations of previous strategy trials by: (1) enrolling patients before catheterization, so that anatomically high-risk patients are not excluded; (2) enrolling a higher-risk patients are not excluded; (3) minimizing crossovers; (4) using contemporary DES and physiologically-guided decision-making [fractional flow reserve analysis (FFR)] to achieve complete ischemic (rather than anatomic) revascularization; and (5) being adequately powered to demonstrate whether routine revascularization reduces cardiovascular death or nonfatal MI in patients with SIHD and at least moderate ischemia. The results of the ISCHEMIA trial will have important implications regarding global guidelines for performance and reimbursement of revascularization procedures in patients with SIHD.

One additional preoperative pathophysiologic substrate that impacts surgical revascularization today much more than before involves the substantial development of the myocardial collateral circulation as a result of the heart's response to MI or even transient myocardial ischemia[31,32]. According to the STS database, approximately 40% of patients revascularized with CABG have a documented prior MI, with many more lacking that documentation or with a history of multiple episodes of ischemia preoperatively. Thus patients coming to surgery today have much more extensive collateralization than in the past. These collaterals have been directly linked to long-term survival in IHD patients, and recently their importance in patients with diabetic microvascular disease has been established[33,34].

In surgical revascularization with CABG, particularly in patients with extensive anatomic and functional disease, these collaterals impact the effectiveness of each individual bypass graft, depending upon the regional myocardial perfusion substrate supplied by that

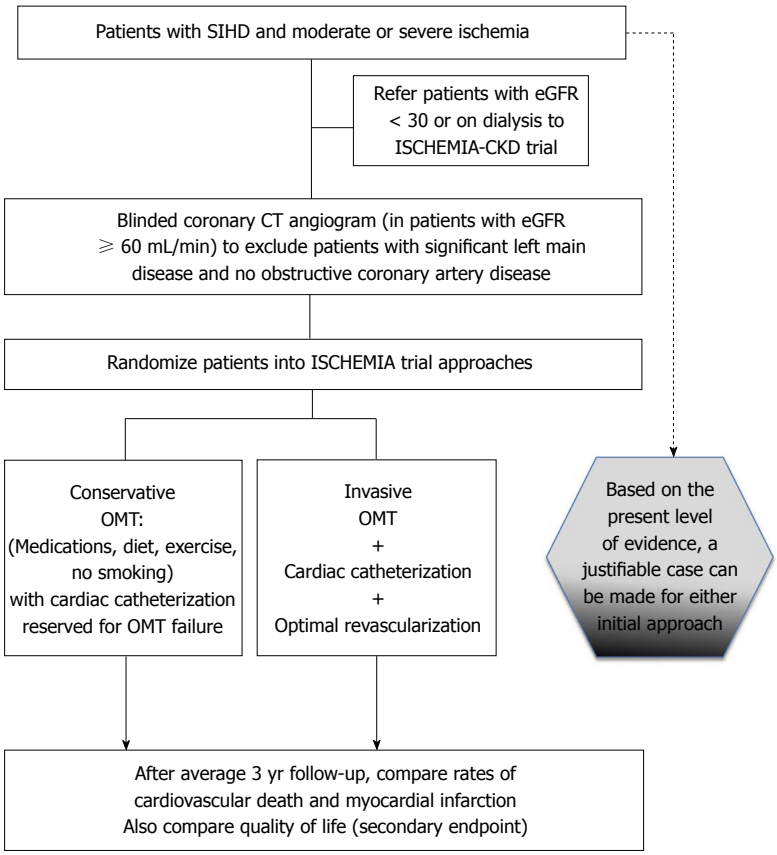

Figure 1 International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (NCT01471522) trial design. After Stone *et al*[17]. CCTA may not be performed with estimated glomerular filtration rate < 60 mL/min. Participants in whom CCTA show significant left main disease (⩾ 50% stenosis) or no obstructive disease are excluded. CCTA results are otherwise kept blinded. ISCHEMIA: International study of comparative health effectiveness with medical and invasive approaches; CCTA: Coronary computed tomographic angiography; eGFR: Estimated glomerular filtration rate; OMT: Optimal medical therapy = guideline-directed medical therapy; SIHD: Stable ischemic heart disease.

graft and the surrounding adjacent substrates[35-37].

Several randomized trial post-hoc analyses have produced data to support the importance of this patho-physiologic substrate in contemporary CABG patients. The Project of *Ex-Vivo* Vein Graft Engineering *via* Transfection IV (PREVENT IV) documented 12-18 mo angiographic follow-up and 5-year clinical outcomes[38]. Vein graft failure in patients on follow-up angiogram was common (43%); in these patients followed for 4 years, clinical outcomes were associated with repeat revascularization, but not with death and/or MI[39]. These data suggest that the myocardium supplied by these occluded vein grafts had enough other blood flow [from the native target vessel epicardial coronary artery (TVECA) and/or collateral flow] so as not to influence the major outcomes of death and MI. In the SYNergy between PCI with TAXus and cardiac surgery (SYNTAX) trial, (ClinicalTrials.gov number NCT00114972)[40] the better outcomes seen in the surgical arm occurred despite a > 40% incomplete revascularization rate at CABG by SYNTAX anatomic criteria[41,42]. Head *et al*[43] documented that incomplete revascularization was associated with adverse outcomes in the PCI cohort but not the CABG cohort. This outcome is impacted by the higher incidence of preoperative MI in the CABG group, and by the greater extent of anatomic disease impacting the underlying myocardial pathophysiologic substrate in these patients. While the revascularization was as complete as technically possible, incompleteness by anatomic criteria alone was likely ameliorated by this dynamic collateral exchange of perfusion in these contemporary surgical revascularization patients.

INTRAOPERATIVE FACTORS AND INFLUENCES

The patient-level benefits of arterial grafting are clear, as IMA grafting to the LAD has been the standard of care for three decades. Despite the overwhelming body of evidence that multi-arterial grafting yields even further benefit for patients, including long-term survival, and freedom from MI, and that bilateral IMA grafting can be safely performed in elderly diabetic patients[44,45], transitioning of the standard of care to this new technical solution has been difficult[11]. Multi-arterial grafting represents a substantial change in the approach and work product of a CABG procedure for the surgeon[9,46]. Therefore, a more thorough understanding of the mechanisms underlying the benefits of multi-arterial grafting is important.

Most randomized trials involving CABG with protocol-specified angiographic follow-up have documented 1 year patency rates for *in-situ* IMA grafts between 95% and 100% at 12-18 mo, with grafting thresholds for angiographic stenoses of 70% or greater[47-50]. The 5% early attrition rate is widely thought to be due to technical errors at surgery[51,52].

Late graft failure following IMA grafting is much more complex in terms of etiology. The "competitive

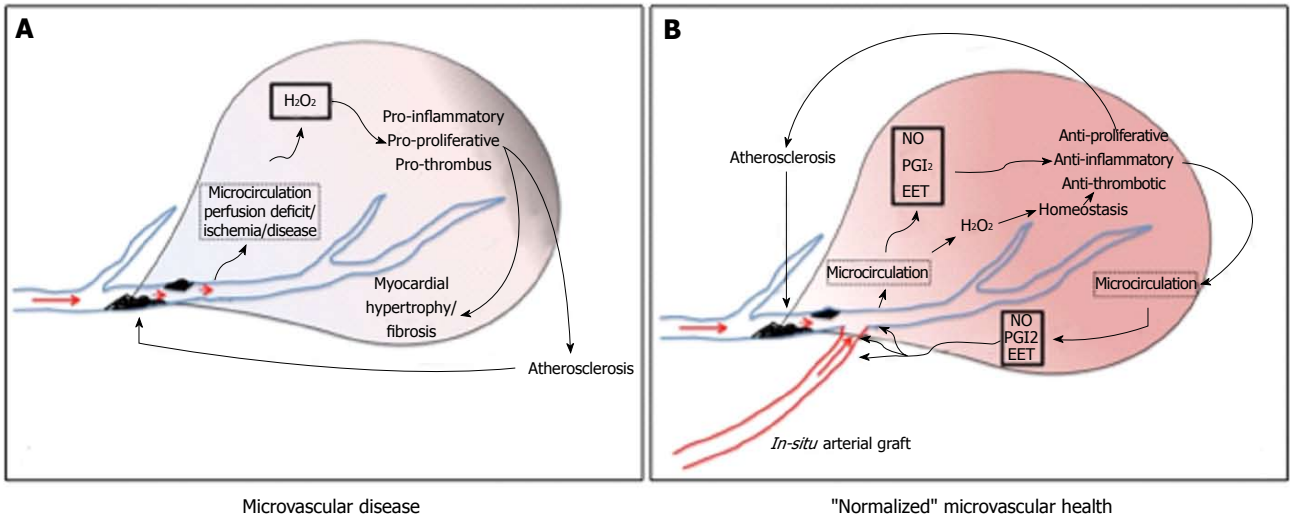

Figure 2 From Ferguson *et al*[37], with adaptation from Gutterman *et al*[62]. In a healthy heart, arteriolar endothelium produces NO, prostacyclin (PGI2, and EETs) as well as low levels of hydrogen peroxide, which support a quiescent non proliferative state. With the onset of disease (A), flow through the microvasculature releases hydrogen peroxide, creating a proinflammatory environment throughout the organ, potentially leading to hypertrophy, fibrosis, and atherosclerosis. In B, with bypass grafting of ischemic myocardium, the microvascular health of the myocardium is "normalized". NO: Nitric oxide; PGI2: Prostacyclin; EET: Epoxyeicosatrienoic acids.

flow" from moderately stenosed native TVECA has been posited as a major cause for late *in situ* IMA graft failure. This is in contradistinction to causes for vein graft failures[53]. Additional causes of late arterial graft failure include factors typically attributed to other conduit failures, such as poor run-off of the distal native coronary circulation, thrombogenic factors, and size mis-match might be factors as well[50]. More recently, computer flow dynamic modeling studies have clarified the role of wall shear stress (WSS) on local hemodynamics, where atheroma are inhibited or retarded under conditions of high shear stress but predisposed to occur under conditions of low shear stress[54-56]. Despite the clinical studies associating intermediate coronary stenoses with increased IMA graft failure, Shimizu *et al*[57] demonstrated that the shear stress of the *in situ* IMA is maintained despite the flow volume being reduced by flow competition. Ding *et al*[58] used computerized flow dynamic modeling to study competitive flow in an IMA-LAD graft model. In this study, they correlated the Time-Averaged WSS and the oscillatory shear index (OSI) with TVECA percent stenosis, and found that TAWSS dropped when the stenosis was < 75%; concomitantly, the OSI distribution increased below 75% stenosis, where high OSI predisposes to endothelial dysfunction and atherogenesis[59], while maintained WSS is responsible for normal endothelial function and endogenous vasodilator production such as nitric oxide (NO).

Further complicating this story is the fact that two myocardial factors influence WSS in TVECAs and arterial conduits as well: Myocardial ischemia resulting from a physiologically significant proximal coronary stenosis increases WSS at the anastomosis and in the vessels, and this increased WSS stimulates the development of collateral circulation through arteriogenesis[60,61]. The influence of myocardial vasculature WSS on conduit and TVECA shear stresses has not been well-characterized.

The reasons for improved long-term patency *vs* other conduits for grafting have been discussed at length in the surgical literature. These include the *in situ* nature of the conduit, endothelial production of endogenous vasodilators NO, prostacyclin (PGI_2) and epoxyeicosatrienoic acids (EETs) to dilate the conduit and protect against the development of atherosclerotic disease in the vessel, better diameter matching between the graft and the TVECA, the absence of atherosclerotic disease and disease progression, and others. In a recent article, Gutterman *et al*[62] characterized the differences between microvascular health and microvascular disease. Figure 2 adapts this concept to the CABG setting, including pre-grafting ischemia (Figure 2A) and post-grafting regional myocardial status (Figure 2B). In "normalized" microvascular health (such as a non-diseased IMA graft in a CABG patient), atherostasis is achieved by predominant endothelial production of these vasodilators (NO, PGI_2 and EET), with anti-proliferative, anti-inflammatory, and anti-thrombotic effects. In disease (such as SIHD), microcirculatory production of reactive oxygen species (H_2O_2) maintains dilation but at the expense of pro-inflammatory, pro-proliferative, and pro-thrombotic responses that contribute to atherosclerosis in TVECAs and hypertrophy and fibrosis in the myocardium. In arteries from healthy subjects, normal WSS activates production of NO to stimulate dilation and vascular homeostasis. Abnormal WSS, vascular stress or the presence of coronary artery disease stimulates the pathological basal level of oxidants and initiates a switch in the mediator of flow-induced dilation from NO to H_2O_2; dilation is maintained (for a time) but at the expense of vascular inflammation and its consequences[62].

Among these, specific relevance to CABG is the

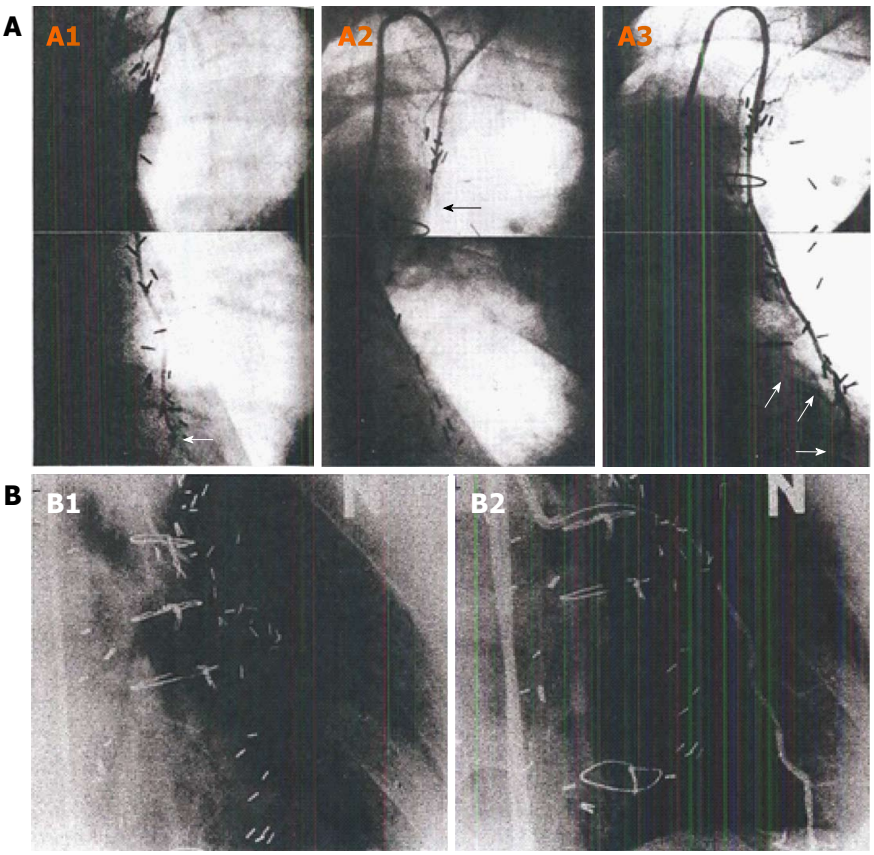

Figure 3 Composite of string sign data. Angiographic documentation of the development of a "string-sign" IMA graft. A: Data from Dincer *et al*[98]. A1: Composite still images from angiogram of IMA-LAD graft at 8 d postop. White arrow show anastomotic site; A2: Composite still images from an angiogram at 1-year postop. Black arrow identifies "string-sign" IMA conduit with little if any distal flow; A3: Composite still images from angiogram at 5 years postop, documenting a widely patent IMA-LAD graft. The three white arrows outline the native TVECA LAD proximal and distal to the anastomosis. There is no angiographic evidence of atherosclerotic disease in the IMA, and no anastomotic evidence of narrowing; B: Data from Kitamura *et al*[99]. Images that clearly illustrate the physiology of arterial conduits. B1: A stringlike LIMA with no-flow into the LAD. Because of the limitations of conventional angiography, flow down the TVECA LAD cannot be simultaneously visualized, but was patent with good antegrade flow; B2: Repeat LIMA arteriography now showing anatomical patency of the graft, as a result of temporary occlusion of the recipient LAD with a percutaneous transluminal coronary angioplasty balloon. The acute influence of anterior wall hypoperfusion immediately translated into resumed functionality of the LIMA graft, documenting the coupling of physiologic IMA flow to the distal regional myocardial physiologic status. IMA: Internal mammary artery; LAD: Left anterior descending coronary artery; TVECA: Target vessel epicardial coronary artery.

endogenous production of vasodilators is believed to be the most important[59,63]. The powerful influence of these physiologic processes has been documented in studies illustrating serial angiographic follow-up after *in situ* IMA grafting. Hartman *et al*[64] and Akasaka *et al*[65] both documented progression from a normal-sized *in situ* conduit, to a string sign several years later, and finally to a supra-normal conduit, as the native coronary circulation and non-arterial bypass grafts developed progressive disease (Figure 3). It is clear from the above discussion that this string sign is not the product of irreversible microvascular disease from vascular inflammation. Rather, it must be an exogenously-stimulated normal endothelial response that can change over time.

In fact, many studies have documented that there is a predictable physiologic response in size and conduit flow in normal *in-situ* arterial grafts not compromised by technical errors over time. In their studies, Shimizu *et al*[57] and Akasaka *et al*[66] hypothesized that competitive flow between the TVECA and the *in situ* graft created the angiographic string sign - a technically angiographically patent graft, where conduit flow was minimal, but which could respond over time by increasing diameter and decreasing flow velocity, improving flow capacity, due to endothelial response triggers.

We now understand more clearly the role that the distal myocardium plays in influencing IMA conduit flow. Our near-infrared fluorescence (NIRF) imaging studies at the time of off-pump beating heart coronary artery bypass (OPCAB) quantified the change in regional myocardial perfusion, if any, associated with anatomically patent bypass grafting, including IMA, vein, and radial arterial grafts (Figure 4). Overall, in 80% of anatomic grafts to arteries with a minimum 70% proximal stenosis, there was a real-time increase in quantified regional perfusion when supplied by the TVECA and the graft conduit, *vs* the TVECA alone[35,37,67]. We believe this perfusion increase was dependent on the physiologic status of the distal myocardium in terms of tissue oxygen and blood flow demand. In the same way, this myocardial status impacts the dynamic flow

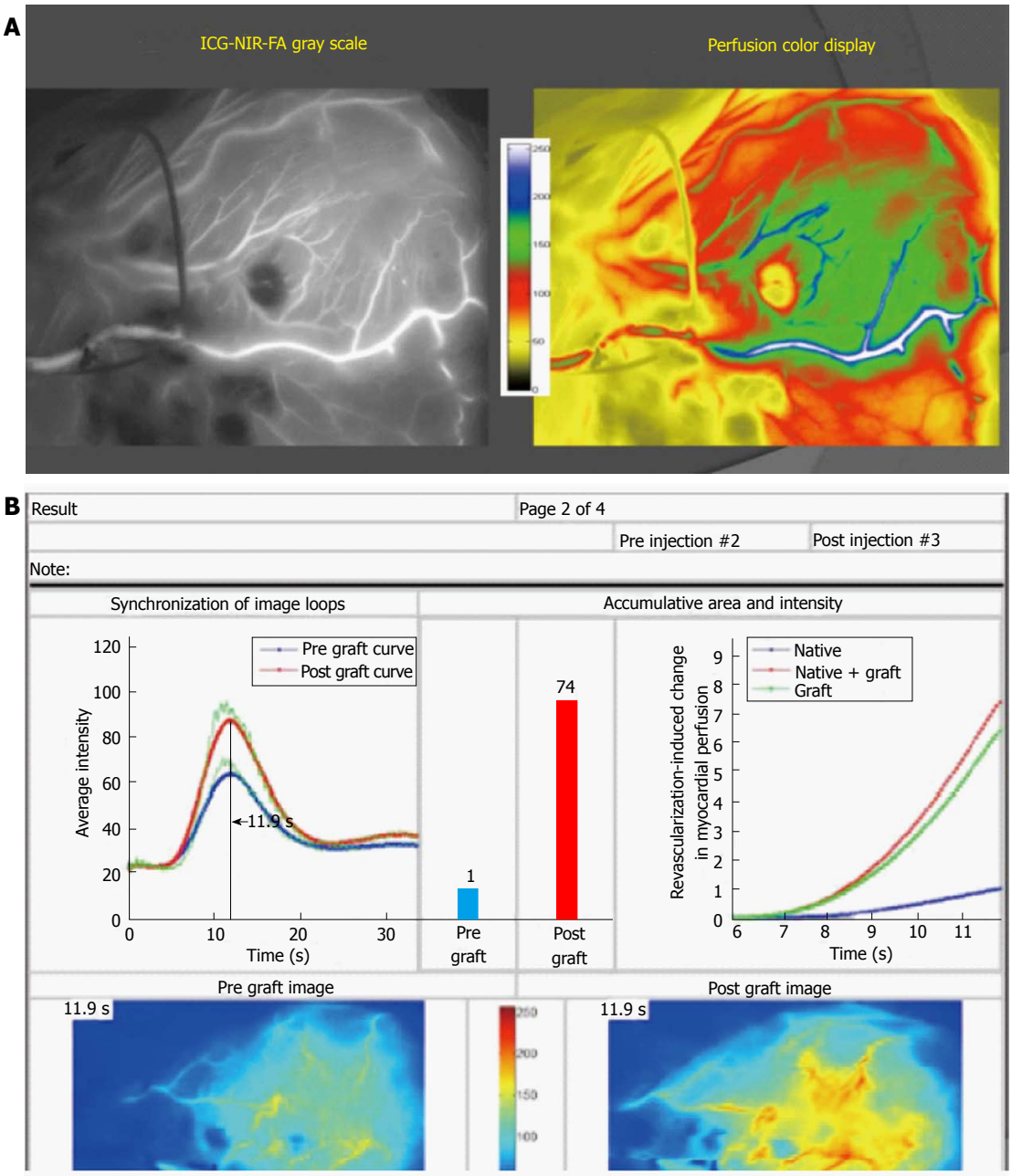

Figure 4 SPY near-infrared imaging of the physiology of revascularization and quantification of the change in regional myocardial perfusion as a result of bypass grafting. A: Near-infrared frame from 34-s video of IMA graft to LAD in 256 grey scale (left panel) and more intuitive color scale (see color bar) to differentiate perfusion differences to the myocardium. The video shows the dynamic arterial and microvascular blood flow interaction between the native TVECA flow and the IMA graft flow in real-time and under true physiologic conditions; B: The Complex Angiography and Perfusion Analysis platform result from and IMA to LAD graft in a patient with prior anterior MI and regional myocardial ischemia preoperatively. The right upper panel quantitatively compares pre-bypass TVECA regional myocardial perfusion (blue line and bar) with post-bypass combination of TVECA + IMA perfusion (red line and bar). The green line in the graph is the relative contribution to perfusion of the IMA graft flow. The two bottom images are synchronized with respect to timing, as shown by the marker on the upper left graph. This patient with anterior ischemia had a 7-fold increase in perfusion to the anterior regional myocardium as a result of IMA grafting. In addition, the proximal LAD in this patient was 100% occluded, and the pre-grafting TVECA perfusion was entirely from flow through lateral and inferior collaterals. IMA: Internal mammary artery; LAD: Left anterior descending coronary artery; TVECA: Target vessel epicardial coronary artery.

characteristics of the *in situ* arterial conduits. Beginning with a technically adequate patent IMA graft, the functionality of the proximal TVECA stenosis (beyond anatomic severity alone) will influence subsequent IMA graft behavior. Early on, the perfusion status of the myocardium impacts early WSS and flow[57]. The pressure drop across the stenosis, if functionally significant, increase shear stress in the myocardial collateral vessels; both ischemia and increased shear stress promote the development of collateralization in the myocardium[60]. In the TVECA, the diminution of flow decreases WSS. If myocardial ischemia is relieved by the combined IMA/TVECA flow, then TVECA WSS is normalized, and the IMA graft accommodates flow

velocity and flow capacity according to its contribution to myocardial demand relief[66]. If the proximal stenosis in the TVECA is not functionally significant, such as described by Ding *et al*[58], then time-averaged WSS of the graft falls, and OSI increases, contributing to the development of a string sign configuration angiographically. This IMA conduit, under new conditions of ischemia, can physiologically respond accordingly to meet this perfusion demand deficit[64]. Over time, as the native TVECA and graft disease progressed, the IMA conduit was driven to supply more and more blood flow to that regional myocardium, resulting in significant vasodilation of the *in situ* conduit. Importantly, this *in situ* conduit likely is supplying blood flow to other regions of the heart as well, given the extent of angiographic disease at this later stage and the assumed presence of extensive collaterals.

From a physiologic perspective, this dynamic nature of *in situ* IMA grafts, coupled to the functional status of the TVECA regional myocardium in a heart with extensive coronary disease and significant collateralization, is a likely physiologic-based explanation for the long-term clinical outcomes benefit from IMA grafting.

Competitive flow is the term used to describe flow interaction between the graft conduit and the TVECA, presumed to occur to a greater extent as the angiographic stenosis in the TVECA lessens. Thus it is presumed that there is more competitive flow to a TVECA with a 50% proximal stenosis than a 70% proximal stenosis. Glineur has reported that this situation of arterial graft competitive flow occurs when conductance (the ability of fluid to transmit through materials) of the graft closely matches that of the native circulation, and is mainly dependent on stenosis severity and on graft diameter and length[68]. However, because intraoperative conventional coronary angiography has not been widely available, and because coronary angiography *per se* does not represent true physiologic conditions, our knowledge about competitive flow in arterial grafts is limited. Moreover, since the behavior of these grafts changes over time, documentation of competitive flow at the time the bypass is created would be useful for understanding its true physiologic impact[69].

Pagni *et al*[70,71] performed a series of animal studies assessing the flow patterns in the graft conduit (IMA and/or vein grafts) and the unobstructed native TVECA. These studies documented four characteristic flow phases during systole and diastole associated with actual competitive flow between the IMA conduit and the TVECA in this experimental setting, without a proximal stenosis (fully competitive flow): In phases 1 and 2, during diastole, there is antegrade flow in both the TVECA and the arterial graft. In early systole, there is antegrade flow in the TVECA but retrograde flow in the distal arterial graft, which reverses in late systole, where there is retrograde flow in the TVECA and antegrade flow in the arterial conduit[70].

The actual flow patterns that occur with more significant proximal stenoses and more severe distal disease are less understood. Gould *et al*[72] demonstrated the relationship between coronary flow reserve (CFR) and isolated coronary stenoses, where CFR was maintained until the stenosis reached 70% or greater. With diffuse anatomic disease, however, this relationship degrades, and "critical" coronary flow reduction becomes prognostic[73]. Ding's simulated competitive flow results in models of the IMA-LAD anastomosis are similar to Gould and Pagni, with a dependency on the degree of proximal stenosis[58]. Using angiographic characteristics, however, Berger[50] concluded that minimal competitive flow occurs until the proximal stenoses is greater than 70% angiographically.

Our extensive studies of bypass grafting in off-pump CABG, where the actual physiology of blood flow in grafts and perfusion to the myocardium has been studied in over 1000 patients on a per graft basis, documented exactly this same reversal of flow pattern as Pagni in angiographically widely-patent IMA grafts to the LAD[67]. However, all these TVECAs (LAD or circumflex marginal branches) had a minimum of 70% proximal stenoses by preoperative angiography (Figure 5). The real-time intraoperative imaging technique was NIRF angiography (SPY, Novadaq Technologies, Toronto, Ontario, CA), coupled with the Complex Angiography and Perfusion Analysis analysis platform developed and patented in our Imaging Laboratory[35]. Importantly, this technology in OPCAB images blood flow and perfusion simultaneously in the TVECAs and graft conduits, and where there are physiologic conditions of coronary flow, coronary pressure, and myocardial functional performance[36].

These clinical studies uncovered two important factors. First, competitive flow was not ever documented angiographically in non-arterial conduits to TVECAs, regardless of the degree of TVECA proximal stenosis, similar to Glineur's data[68]. Presumably, at the time of surgery, the flow down vein grafts free of technical problems is so dominant that even with intermediate (40%-70%) stenosis in the TVECA, competitive flow doesn't occur. Second, in a sub-study of *in situ* IMA conduits to TVECAs with a 70% or greater proximal stenosis on the L side of the heart (LAD, circumflex marginal branches), a total of 23% of IMA grafts did not improve regional myocardial perfusion. That is, the post *vs* pre quantified distal regional myocardial perfusion (Figure 4) didn't increase, despite a widely patent anastomosis angiographically and the absence of any clinical signs of incomplete relief of regional hypoperfusion/ischemia, or hemodynamic instability[67]. Examination of the real-time image sequences from these 23% *in situ* IMA grafts documented that > 80% had NIRF angiography documented competitive flow by these Pagni criteria.

These objective, imaging-based data document that competitive flow in arterial grafts does occur with

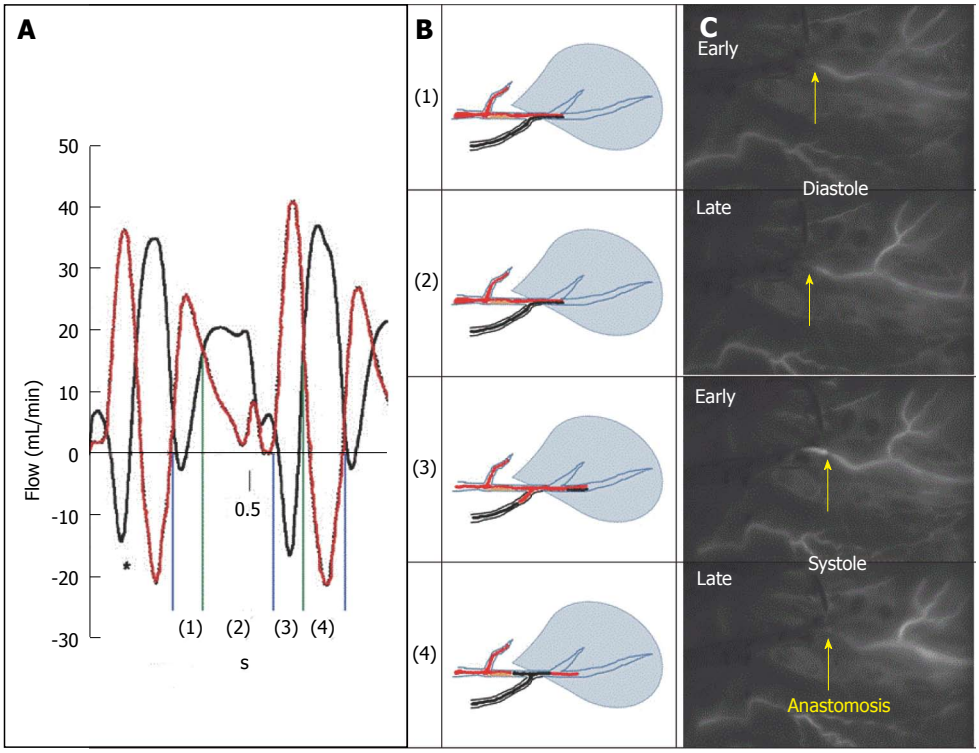

Figure 5 Intraoperative real-time documentation of competitive flow in arterial internal mammary artery-left anterior descending coronary anastomosis with > 70% stenosis. Competitive flow documented in *in situ* arterial graft to TVECA with > 70% proximal stenosis. A: Dynamic flow data from Pagni *et al*[71] illustrating flow in IMA (red) and LAD (black) in an experimental model of competitive flow where the LAD has no proximal stenosis (maximal competitive flow). In phases 1 and 2, during diastole, there is antegrade flow in both the TVECA and the arterial graft. In early systole, there is antegrade flow in the TVECA but retrograde flow in the distal arterial graft, which reverses in late systole, where there is retrograde flow in the TVECA and antegrade flow in the arterial conduit; B: Diagrammatically the IMA-LAD interaction at the anastomosis in this patient; C: Four still frames taken from the 34-s video of this bypass graft using near-infrared imaging technology (SPY, Novadaq Technologies, Toronto, Ontario, CA). The arrow indicates the site of the anastomosis. The four frames are in temporal sequence but not consecutive frames; they are selected at the four diagram points indicated at the middle panel. Each diagram point is taken from the appropriate time-point within each of the four intervals (early diastole, late diastole, early systole, late diastole). This real-time intraoperative imaging shows identical flow patterns as demonstrated in the Pagni experimental model, despite the proximal > 70% stenosis. IMA: Internal mammary artery; LAD: Left anterior descending coronary artery; TVECA: Target vessel epicardial coronary artery.

proximal stenoses of 70% or greater severity at a much higher frequency that presumed based on indirect data as reported[74,75]. These data also strongly support the concept that the flow interaction between the *in situ* conduit and the TVECA is in fact less influenced by the proximal stenosis severity (anatomy) and more influenced by the physiologic status of the distal regional myocardium in terms of perfusion deficit and regional myocardial ischemia. As discussed above, based on these physiologic factors the arterial conduits will adapt to meet these demands over time and to the degree possible[66,69]. Nordgaard *et al*[76] demonstrated in an experimental model that WSS and OSI of an IMA graft was affected by the degree of competitive flow, where high competitive flow produced unfavorable WSS conditions consistent with endothelial dysfunction and subsequent graft narrowing and failure. However, the severity of competitive flow was based on percent proximal stenosis, and did not account for the functionality status of the stenosis.

These intraoperative imaging findings, in fact, are supported by the critically important developments over the past decade in PCI revascularization, based on the numerous studies with FFR and instantaneous wave free (iFR) studies[77-82]. In the FFR *vs* Angiography for Multivessel Evaluation (FAME) (ClinicalTrials.gov, No. NCT00267774) 1 study, 20% of angiographic stenoses between 70% and 90% were determined to be non-functional stenoses, consistent with our OPCAB studies[77]. Moreover, as presented by Stone *et al*[17], the physiologic status of the myocardium in patients with SIHD, and the ability of OMT to influence that status, creates equipoise in determining a conservative *vs* interventional therapeutic approach to patients, even with documented moderate-to-severe ischemia prior to therapy initiation. Importantly, in this context PCI and CABG are considered alternative forms of revascularization intervention determined by current RCT data from the head-to-head SYNTAX[42] and Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) (ClinicalTrials.gov number NCT00086450) trials[83]. However, the fact that they are alternative revascularization strategies means that the physiologic substrate for that intervention is equivalent, from a physiologic perspective. Our data strongly support the

importance of physiology in determining short-term and long-term outcomes from surgical revascularization, in parallel to this experience in percutaneous revascularization[36]. In addition, others have described the current potential role of FFR-guided CABG, further emphasizing the emerging importance of physiology in revascularization[84].

In addition, recent data from SYNTAX examining the causes of death following PCI *vs* CABG in complex CAD emphasized the importance of the physiological impact of revascularization on the myocardial substrate in complex CAD[85]. CABG was associated with a significantly reduced rate of MI-related death, indicating that the anatomically-incomplete but functionally complete CABG revascularization provided sustained global perfusion and protection from subsequent ischemic events (*e.g.*, MI), in part because of the collateralization associated with more extensive severity of CAD.

Importantly, the emerging call for multi-arterial revascularization to become the "standard of care" for contemporary CABG fits tightly into this strategy. Because of the findings outlined here, the concept of "complete anatomic revascularization" must be revised into "reasonable incomplete revascularization"[86,87]. A multi-arterial strategy may be initially thought to limit the number of potential grafts, producing incomplete revascularization, at least from an anatomic perspective. However, recognizing the importance of physiology in surgical revascularization, including the functional nature of the proximal stenoses, physiologic status of the distal regional myocardium *vs* assumed competitive flow, understood dynamic nature of the *in situ* arterial conduit, and the existence of collateral flow in the myocardial substrate being operated upon, allows for more specific design of a revascularization strategy using arterial conduits that will remain beneficial over the long-term.

POSTOPERATIVE FACTORS AND INFLUENCES

The current results, based on clinical outcomes, from CABG intervention in patients with moderate and severe SIHD by anatomic criteria are excellent, and clearly are preferable to OMT and PCI interventions in the correct patient population[88]. Overall, however, the 25-plus year decline in risk-adjusted 30-d mortality for CABG, despite the concomitant increase in predicted operative risk, has plateaued over the past 5 years (STS database) at approximately 2%. This plateau is so distinct from the prior trend that it is appropriate to query why this might be the case[89]. Is 2% "as low at is feasible", given the current population coming to CABG? Is the relative impact of collecting and sharing clinical outcomes data on continuous quality improvement efforts lessened at this level of high-performance? Or is risk-adjusted mortality as a benchmark for quality no longer effective at this high-performance level[45]?

An alternative perspective is that current standard outcomes are not granular enough to drive further quality improvements, as has been demonstrated previously with the infrastructure of the STS National Database[90,91]. Other metrics, in addition to existing ones, are needed to further drive clinical improvements in outcomes. It may well be that these physiologic aspects of revascularization (preoperative, intraoperative and postoperative), along with intraoperative documentation of technical quality and the absence of surgeon error represent the new metrics needed to drive quality improvement in the future.

One area where the impact of quality improvement interventions remains to demonstrate its effectiveness is in the area of secondary prevention of SIHD following CABG. Based on then-contemporary data from other areas of cardiovascular medicine therapy, we documented in the largest randomized clinical trial of continuous quality improvement to date the effectiveness of dissemination of information, local quality improvements and the infrastructure of a national database the increased adoption of secondary prevention measures [ASA, beta-blocker, statin, and ACE inhibitor therapy (in appropriate patients)] following CABG[91]. This study covered a time interval that was relatively early in the statin era, and while the adoption at > 400 surgical centers across the United States increased for each measure and the composite of all measures, the adoption of post-operative statin therapy was the most dramatic.

Since the Achilles' heel of CABG has been the late development of atherosclerotic disease in vein graft conduits (in patients operated upon 15-50 years ago)[53], the full effect of this postoperative statin intervention still remains to be evaluated. Importantly, the benefits of statin therapy in non-surgical patients with SIHD are incontrovertible[92]. However, if the anti-atherosclerotic effects of statins in CABG mirror the effects in other settings of IHD, this intervention should impact long-term outcomes by retarding the development of disease progression in CABG patients[93]. Other pleiotropic effects of statins have been advocated as beneficial in CABG patients as well[26,92].

In an important recent study, however, room for improvement and justification for that improvement was highlighted. Iqbal *et al*[94] studied the use of OMT in patients with complex coronary disease undergoing revascularization in SYNTAX, and addressed the long-term significance of these use patterns. OMT was defined as the combination of at least one antiplatelet drug, statin, beta-blocker and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. OMT was underused in all revascularization patients, especially in the CABG group. In five-year outcomes analyses, OMT was an independent predictor of survival, including mortality and the composite end-point of death/MI/stroke. The treatment effect with OMT (36% relative reduction over 5 years) was greater than the treatment effect of the revascularization strategy (26% relative

reduction in mortality with CABG *vs* PCI over 5 years). All components of OMT were important for reducing adverse outcomes in both revascularization strategies. Clearly, contemporary cardiac surgery must continue to aggressively incorporate this life-sustaining physiologic intervention in post-CABG patients, no only for the first six weeks but work with all cardiovascular providers to make sure this intervention is sustained indefinitely following CABG[17].

One area of continuous evolution in secondary prevention is the utilization of dual anti-platelet therapy (DAPT) following CABG, and in particular in the approximately 18% of CABG cases performed using the OPCAB technique. The AHA/ACC/STS recently updated the guidelines for Secondary Prevention Following CABG, in particular with reference to DAPT. At the same time, the Guidelines on duration of DAPT in patients with Coronary Artery Disease has been updated as well[95]. The recent introduction of other new anti-platelet agents may result in the emergence of an improved DAPT strategy. Thus this post-operative secondary prevention arena following CABG will continue to evolve, as the full impact of statin therapy and DAPT therapy becomes evident. Again, the effects of these agents in modifying the physiology of atherosclerosis and platelet actions drives new potential improvements in clinical outcomes in CABG[95].

The STS has recently published Clinical Practice Guidelines on Arterial Conduits for Coronary Artery Bypass Grafting[96]. This excellent, technically and anatomically focused Guideline recommending that use of arterial grafts (specific targets, number, and type) should be a part of the discussion of the heart team in determining the optimal approach for each patient. This physiologic discussion provides in part the underlying scientific support for that recommendation.

Finally, this emerging granularity of the physiologic circumstances and effects of revascularization in CABG promises to have a similar impact as FFR/iFR have had on PCI intervention: The generation and incorporation of an entire body of new knowledge, which has benefitted both revascularization strategies. Thus far, these data presented here have produced a new definition for the goal of CABG, namely, to relentlessly restore blood supply, by both anatomic and physiologic criteria, to all areas of myocardium possible for the longest interval of time possible. "What we don't know" represents the future[97].

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MINIREVIEWS

Mechanisms and clinical significance of early recurrences of atrial arrhythmias after catheter ablation for atrial fibrillation

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Abstract

Early recurrence of atrial arrhythmias (ERAA) after ablation is common and strongly predicts late recurrences and ablation failure. However, since arrhythmia may eventually resolve in up to half of patients with ERAA, guidelines do not recommend immediate reintervention for ERAA episodes occurring during a 3-mo post-ablation blanking period. Certain clinical demographic, electrophysiologic, procedural, and ERAA-related characteristics may predict a higher likelihood of long-term ablation failure. In this review, we aim to discuss potential mechanisms of ERAA, and to summarize the clinical significance, prognostic implications, and treatment options for ERAA.

Key words: Atrial fibrillation; Recurrence; Catheter ablation; Pulmonary vein isolation

Core tip: There have been several studies examining the predictors of early recurrences of atrial arrhythmias (ERAA) during the blanking period after atrial fibrillation (AF) ablation and the predictive value of such early recurrences on late recurrences. In this review, we summarize the mechanisms and predictors, clinical significance, prognostic implications, and treatment options of ERAA after AF ablation.

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INTRODUCTION

Catheter ablation is an effective treatment option for patients with symptomatic atrial fibrillation (AF). The

cornerstone of AF ablation involves pulmonary vein isolation (PVI). Early recurrences of atrial arrhythmia (ERAA) are frequent in the post-ablation period, and may occur as either AF or organized atrial tachycardia (OAT), and in some instances may resolve over time without requiring repeat intervention. These early recurrences are thought to be related to post-ablation inflammation, edema, and healing. As such, the consensus guideline statements have recommended employing a 3-mo "blanking period" after AF ablation during which AF or OAT recurrences should not be considered as ablation failure[1]. In this review, we will define and discuss the implications of ERAA, as well as summarize the literature with regards to methods to prevent and treat ERAA.

BLANKING PERIODS AND EARLY RECURRENCES

The use of a blanking period has been employed under the assumption that not all ERAA episodes results in late recurrences. The 2012 HRS/EHRA/ECAS expert consensus statement recommends the use of a 3-mo blanking period after ablation, during which time ERAA episodes not be classified as treatment failure. However, the authors of the guideline statement do state that the use of a shorter blanking period (< 3 mo) is acceptable as long as it is pre-specified and described in the study methods[1]. In line with the consensus statement, most operators tend to avoid repeat ablation for ERAA occurring within the blanking period unless patients are extremely symptomatic with recurrences which are refractory to antiarrhythmic drugs (AADs) and repeated cardioversions.

Variable blanking periods have been utilized across published studies, ranging anywhere from 72 h up to 3 mo post-ablation[2]. While the HRS/EHRA/ECAS consensus statement selected 3 mo as the blanking period of choice, the optimal blanking period to maximize the sensitivity and specificity of prognostic implication of ERAA- and therefore the optimal cutoff interval during which early re-ablation should be avoided, remains poorly studied.

DETECTION OF ERAA IN THE BLANKING PERIOD

Methods of monitoring used to detect ERAA episodes have varied between studies. There is a wide range of intensiveness with regards to duration and strategy of monitoring, and detection of ERAA is dependent on type of monitoring post-ablation. The least intensive monitoring strategies involve symptom-driven 12-lead electrocardiogram, and 24-h or 48-h Holter monitoring ordered only when patients endorse symptoms of palpitations or notice an abnormal pulse. More intensive strategies which studies have utilized include handheld symptom-driven rhythm monitor applications, 30-d transtelephonic monitors, and auto-triggered external and implantable subcutaneous loop recorders. Landmark trials in patients with cryptogenic stroke have demonstrated that more intensive rhythm monitoring for longer durations using transtelephonic monitoring devices (*i.e.*, CardioNet, Malvern, PA; LifeWatch, Rosemont, IL; Medicomp, Melbourne, FL) or implantable cardiac monitors (*i.e.*, Reveal XT and Reveal LINQ; Medtronic, Minneapolis, MN) may increase the likelihood of detecting asymptomatic AF[3,4]. However, since most operators tend to avoid early reablation for paroxysmal recurrences of asymptomatic ERAA during the blanking period, the optimal method of post-ablation monitoring (or whether any monitoring is necessary at all, for that matter) remains controversial.

FREQUENCY OF ERAA

In a pooled analysis by Andrade *et al*[2], the incidence of ERAA after radiofrequency catheter ablation across multiple studies utilizing a 3-mo blanking period ranged from 16%-67% with a mean pooled estimate of approximately 38%. The incidence of ERAA is highest immediately post-ablation and tends to decrease over time throughout the blanking period[5,6]. Rates of ERAA appear to be similar after ablation with radiofrequency or cryoablation, although there may be differences in the predictive value of inflammatory responses on the incidence of ERAA post-ablation between techniques.

For example, in the multicenter Sustained Treatment of Paroxysmal Atrial Fibrillation trial, which randomized patients with paroxysmal AF to medical therapy *vs* PVI with cryoballoon ablation, 51% of patients treated with cryoablation experienced ERAA within the first 3 months post-ablation, and those with ERAA (*vs* without ERAA) were significantly more likely to experience late recurrence (55.6% *vs* 12.7%; $P < 0.001$)[7].

Ciconte *et al*[8] studied 100 patients with persistent AF treated with PVI using second-generation cryoballoon *vs* radiofrequency ablation and found that the rates of both ERAA (51.9% *vs* 48.1%; $P = 1.0$) and late recurrence (47.6% *vs* 52%; $P = 0.84$) were similar between ablation technologies. Among all patients, ERAA in their study predicted late recurrence with a hazard ratio of 6.31 (CI: 3.37-11.83, $P < 0.01$).

In a nonrandomized fashion, Miyazaki *et al*[9] prospectively examined 82 consecutive patients with paroxysmal AF treated with PVI using either radiofrequency ablation *vs* cryoablation with the second generation cryoballoon. While the peak hs-CRP level was similar between ablation techniques, the level of hs-CRP 2 days post-ablation predicted development of ERAA in those treated with radiofrequency (HR = 1.7; 95%CI: 1.01-2.87; $P = 0.048$) but not cryoablation, suggesting that degree of inflammatory marker response may have a stronger predictive value for ERAA after radiofrequency compared with cryoablation.

Table 1 Characteristics which are predictive of the development of early recurrences of atrial arrhythmias after atrial fibrillation ablation

Clinical characteristics
Older age[5]
Male gender[7]
Hypertension[5]
Structural heart disease[10,20]
Longer AF duration[5]
Nonparoxysmal AF type[5]
CHA2DS2-VASc, R2CHADS2 scores[11]
Imaging characteristics
Left atrial size/volume[5]
Right atrial size/volume[12]
Left ventricular size/volume[13]
Left ventricular systolic dysfunction[14]
Left ventricular diastolic dysfunction[15]
Left atrial epicardial adipose tissue[16]
Ablation procedural characteristics
Incomplete PVI[13,20]
AF inducibility[21]
Multiple AF foci[10]
LA free wall AF foci[10]
Lack of AF termination during procedure[22]
Lack of SVC isolation[5]
Inflammatory markers
Higher body temperature post-ablation[17]
C-reactive protein[17]
Homocysteine[18]
Increased LA roof thickness with delayed enhancement MRI 24 h post-ablation[19]

Table modified from Andrade *et al*[2]. AF: Atrial fibrillation; PVI: Pulmonary vein isolation; MRI: Magnetic resonance imaging.

PREDICTORS OF ERAA

Prior studies have identified clinical and demographic characteristics, arrhythmia characteristics, electrocardiographic and echocardiographic characteristics, and AF ablation procedural and post-procedural characteristics which are predict the development of ERAA after ablation, several of which we have listed in Table 1[2,5,7,10-22].

MECHANISMS AND PATHOPHYSIOLOGY OF ERAA

The incidence and clinical significance of ERAA after surgical MAZE is strikingly similar to that of catheter ablation. Approximately 50%-60% of patients develop in-hospital ERAA after MAZE, and those with ERAA have a higher rate of late recurrence (30%) *vs* those whose hospital course is not complicated by ERAA (5%-10%)[23,24].

The mechanism of ERAA after catheter ablation probably differs from that of late recurrences, and is likely dependent on the initial ablation strategy. In patients with paroxysmal AF treated with limited ablation strategies focused primarily on achieving PVI, we have found that late recurrence is usually due to chronic reconnection of previously isolated PVs. In patients with persistent AF treated with empiric linear ablation or those who undergo more extensive substrate-based ablation, gaps in lines may predispose to the development of late macroreentrant OATs. ERAA within the first 7 d post ablation occurs in the setting of an intensely inflammatory milieu. As such, it is difficult to differentiate in the early post-ablation period whether ERAA results from transient post-ablation inflammation (which is likely to resolve without the need for repeat ablation) *vs* chronic PV reconnection. Furthermore, using a rigorous trigger induction protocol, we have identified that non-PV triggers of AF may exist in 11% of patients presenting for AF ablation[25]. Thus the persistence of non-PV triggers due to inadequate identification and elimination of non-PV triggers during the initial ablation procedure can allow for both ERAA and late recurrences to occur.

Lim *et al*[26] measured the blood concentration of several inflammatory markers (hs-CRP, Troponin T, CK-MB, fibrinogen, and D-dimer) before ablation, and serially at different time periods (1, 2, 3, 7 d, and 1 mo) after ablation and correlated the degree of inflammatory marker elevation with AF recurrence documented at different time points post-ablation. They found that the degree of elevation of hs-CRP, troponin-T, and fibrinogen predicted ERAA within 3 d post-ablation, but not at 3 or 6 mo.

Das *et al*[27] examined the association between timing of ERAA with the likelihood of PV reconnection at repeat electrophysiology study in 40 patients with nonparoxysmal AF treated with PVI. After the index ablation procedure, all 40 patients were brought back for electrophysiology study regardless of whether they had recurrence post-ablation. The operator was blinded to the presence and timing of ERAA, and all PVs were assessed for reconnection using a circular mapping catheter. All identified sites of reconnection were related to reisolate PVs, regardless of the presence or absence of ERAA. In total, 17 (42%) of the patients had ERAA within the first 2 months after ablation, preceding the repeat electrophysiology study. The authors found that ERAA occurring within the second month was strongly associated with PV reconnection, and also strongly predicted "extensive reconnection" of $\geqslant$ 2 PVs. Contrarily, ERAA limited to the first month post-ablation had no association with PV reconnection. The results of the study suggested that ERAA within the first month was more likely to be related to transient factors such as inflammation, temporary autonomic imbalances, and the time-course of lesion formation, while ERAA occurring after the first month was more likely to represent ablation failure and PV reconnection[28].

Ablation strategies

The initial ablation strategy may affect the prognostic implications of ERAA. With approaches which involve more extensive substrate-based ablation, ERAA is more likely to be related to edema and inflammation, and accordingly may be more likely to resolve with

time. Meanwhile, ERAA in patients treated with less extensive ablation approaches mainly (*i.e.*, targeting PV and non-PV triggers, for example), may be more likely to represent PV reconnection or inadequate trigger elimination. Since these triggers are unlikely to resolve spontaneously without intervention over time, eventual reablation may be necessary for these patients to achieve freedom from AF.

Post-hoc analysis of data from the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation trial [which compared PVI alone, ablation of complex fractional atrial electrograms (CFAE) alone, and PVI plus CFAE] showed that patients treated with PVI alone who experienced ERAA (*vs* those without ERAA) had significantly higher rates of late recurrence[29]. Interestingly, the predictive value of ERAA on late recurrence was not as strong among those treated with CFAE or PVI plus CFAE. This suggests that substrate-based approaches involving extensive ablation may cause higher incidence of AF related to acute reversible changes post-ablation.

We at our institution employ a strategy aimed at elimination of PV and non-PV triggers. In our experience, patients with recurrent AF after ablation who present for repeat ablation nearly always have PV reconnection and/or non-PV triggers[30]. Non-PV triggers which were not targeted during the initial ablation may manifest as PACs during the ERAA period post-ablation, and may predict late AF recurrence. Gang *et al*[31] examined 7-d Holter monitors in 124 patients six months post-PVI (3 mo after the blanking period had ended) and found that frequent premature atrial complexes (PACs) strongly predicted late AF recurrence. Patients who developed late recurrence had a median of 248 PACs per day compared *vs* those without late recurrence (77 PACs per day). Based on receiver operating characteristic curve analysis, the authors calculated that the presence of $\geqslant$ 142 PACs/d predicted late AF recurrence with a hazard ratio of 2.84 (95%CI: 1.26-6.43; P = 0.01). While their study did not examine the predictive value of PACs during the ERAA blanking period, one could hypothesize that atrial ectopy originating from PV and non-PV foci manifesting as PACs during the blanking period might represented inadequately targeted triggers or partial PV reconnection.

ERAA CHARACTERISTICS WHICH PREDICT LATE RECURRENCE

The occurrence of ERAA after ablation is well known to be a strong independent predictor of late recurrence and long-term ablation failure. In the pooled analysis of several studies by Andrade *et al*[2], there was a 53.7% late recurrence rate among patients with ERAA compared *vs* only 6.9% in patients without ERAA. Several studies have examined whether certain types of ERAA (AF *vs* OAT or atrial flutter) are more predictive of late ablation success. While some authors have suggested success rates after repeat ablation in patients who recur as OAT (*vs* AF) after their initial ablation attempt, it remains unclear whether OAT in the ERAA period is more or less predictive of late ablation failure[32].

Nalliah *et al*[33] examined 119 consecutive patients with paroxysmal or persistent AF who underwent ablation with PVI and additional ablation (50% underwent mitral isthmus linear ablation, and 18% had additional CFAE ablation) to determine the impact of AF and OAT occurring within the blanking period. Patients were not closely monitored for asymptomatic AF during the blanking period, but ERAA as AF was detected in 28% and OAT in 25% within the 3 mo blanking period. Overall, early AF predicted late AF (HR = 3.53; 95%CI: 1.72-7.29; P = 0.001) and early OAT predicted late OAT (HR = 5.62; 95%CI: 2.88-10.95; P < 0.0001). Interestingly, early AF did not predict late OAT, and early OAT did not predict late AF. The authors also found that AF and OAT occurring in the third month of the blanking period had different predictive values for late recurrence: AF in the third month predicted late AF, although OAT in the third month did not predict late OAT.

We do not routinely do empiric linear ablation at our institution, and the majority of patients experiencing ERAA after ablation have AF only (71%; *vs* 5% with early OAT only and 24% with both early AF/OAT)[28]. In our experience, we have found no differences in the likelihood to develop late recurrences based on ERAA type (AF *vs* OAT) (P = 0.92). Since we employ a limited ablation strategy limited to antral PVI and targeting of non-PV triggers, it is possible that in patients treated with more extensive substrate-based ablation approaches involving linear or CFAE ablation, the presence of ERAA as OAT may suggest the presence of gaps in the ablation lines or incomplete CFAE ablation, resulting in late OAT, frequently necessitating repeat ablation.

The predictive value of ERAA appears to be dependent on both frequency and timing of ERAA within the blanking period. We have shown that in patients treated with a limited ablation strategy focused on PVI and elimination of non-PV triggers, the predictive value of ERAA episodes during the first 6 weeks post-ablation is quite variable based on these factors[28]. In our study, we divided the 6-wk blanking period into three separate intervals (Early: weeks 1-2; Intermediate: weeks 3-4; and Late: weeks 5-6), and found that patients with ERAA in a single interval (OR = 3.2, 95%CI: 1.7-5.8 *vs* no ERAA) are significantly less likely to have late recurrence within 1 year *vs* those with ERAA spanning over multiple intervals (OR = 14.6, 95%CI: 7.3-29.6).

Mugnai *et al*[34] have shown similar prognosis of late ERAA within the blanking period after ablation for paroxysmal AF using second-generation cryoballoon ablation instead of radiofrequency energy. In their study of 331 consecutive patients treated with cryoballoon ablation, all patients with ERAA occurring in the second half of the 3-mo blanking period experienced subse-

quent recurrences after the blanking period- suggesting that ERAA occurring later within the blanking period are more predictive of ablation failure[34].

Willems *et al*[35] recently reported the results of a predefined secondary analysis of the prospective, randomized Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination trial where the authors analyzed the significance of ERAA at different times throughout the 3-mo blanking period in predicting late recurrences. They divided ERAA which occurred during month 1, 2, and 3 of the blanking period and found that the 1-year ablation success rate was significantly higher among patients without ERAA (77.2% 1-year freedom from AF), while success rates decreased as ERAA occurred later within the blanking period: 62.6% ERAA in month 1, 36.4% in month 2, and 7.8% in month 3 ($P < 0.0001$), with HR = 1.84 for month 1, 4.45 for month 2, 9.64 for month 3. The authors identified a blanking period of 50 d to yield the greatest discriminatory potential by reviewer operating characteristic analysis, and given the dismal (> 90%) late recurrence rates among patients with ERAA during month 3, the results of this study question whether the 3-mo blanking period should be revised.

PREVENTION OF ERAA

AADs

A number of studies have demonstrated that the use of AADs after ablation reduces the incidence of ERAA and reduces hospitalizations and cardioversions during the blanking period. However, meta-analyses have shown that long-term ablation success remains unaffected by early AAD use[36-38]. This would suggest that AADs might mask the early indicators of failed ablation, which may be allowed to manifest only once AADs are withdrawn. While this may indeed decrease hospitalization rates and healthcare expenditure, it may also simply be delaying the recognition of ablation failure.

The Antiarrhythmics After Ablation of Atrial Fibrillation (5A Study) Randomized 110 patients with PAF to AAD (propafenone, flecainide, sotalol, or dofetilide) *vs* no AAD after AF ablation[39]. Those in the AAD group were less likely to have sustained AF recurrence (> 24 h), AF-related hospital admission, cardioversion, AAD adjustment or drug intolerance (19% *vs* 42%; $P = 0.005$ for primary composite endpoint) six-week post ablation.

The Efficacy of Antiarrhythmic Drugs Short-Term Use After Catheter Ablation for Atrial fibrillation trial was a multicenter prospective randomized controlled trial which compared the use of AADs for 90 d post ablation *vs* control in patients after catheter ablation for paroxysmal AF[40]. The authors aimed to examine whether prevention of ERAA with AADs would promote LA remodeling and therefore improve long-term ablation success. They enrolled 2038 patients (1016 randomized to AADs, 1022 control) and the primary endpoint was AF recurrence (lasting > 30), need for repeat ablation, hospitalization, or use of class Ⅰ or Ⅲ AAD at 1 year. They found that although those in the AAD group were more likely to be free from AF during the 90-d treatment period (59% *vs* 52%; HR = 0.84, 95%CI: 0.73-0.96; $P = 0.01$), there was no difference in any of the primary outcome measures at 1 year post-ablation.

The recurrence of arrhythmia following short-term oral AMIOdarone after CATheter ablation for atrial fibrillation trial was a two-center double-blind, randomized placebo-controlled trial which randomized 212 patients with paroxysmal or persistent AF treated with AF ablation to 8 wk of oral amiodarone *vs* placebo following catheter ablation[41]. The authors aimed to determine whether temporary amiodarone use post-ablation would decrease both early and late recurrences. Patients in the amiodarone group had significantly lower rates of ERAA within the blanking period (34% *vs* 53%; $P = 0.006$) but there was no difference in rates of late recurrence at 6 mo between groups (39% *vs* 48%; $P = 0.18$). Additionally, AF-related hospitalization (RR = 0.43, 95%CI: 0.23-0.77, $P = 0.006$) and the need for cardioversion (RR = 0.36, 95%CI: 0.20-0.62, $P = 0.0004$) within the blanking period was significantly reduced in those treated with short-term amiodarone-driven mainly by those with persistent AF, as demonstrated in a subgroup analysis.

Anti-inflammatory agents: Corticosteroids and colchicine

The pro-inflammatory milieu in the immediate post-ablation period is thought to contribute to the development of ERAA, thus many investigators have examined the utility of anti-inflammatory agents to prevent inflammation-induced ERAA. The two major pharmacologic anti-inflammatory agents which have been studied include corticosteroids and colchicine.

Studies examining the use of steroids post-ablation to reduce ERAA have produced conflicting results. Koyama *et al*[42] randomized 125 patients with PAF to steroids (2 mg/kg IV hydrocortisone given immediately post-procedure, followed by 0.5 mg/kg per day oral prednisone for 3 d) *vs* placebo and found that patients randomized to treatment with corticosteroids were less likely to have ERAA within 3 d (7% *vs* 31%), but had similar rates of ERAA between days 4-30. Kim *et al*[43] randomized 138 patients to treatment with steroids *vs* control after ablation. Patients randomized to steroids in their study were treated with intravenous methylprednisolone (0.5 mg/kg per dose) for 2 d followed by 12 mg of oral methylprednisolone for 4 d. Those treated with steroids had a lower rate of ERAA in the 3 mo blanking period (23.4% *vs* 48.6%, $P = 0.003$) but there was no difference in late recurrence rate up to 24 mo ($P = 0.918$). In their multivariate model, the use of steroids was independently associated with lower rate of ERAA (OR = 0.45; 95%CI: 0.25-0.83, $P = 0.01$).

The anti-inflammatory agent colchicine has also been tested as an antiarrhythmic agent to prevent ERAA after AF ablation. In a double-blind fashion, Deftereos

et al[44] randomized 80 patients with paroxysmal AF to colchicine (0.5 mg twice daily for 3 mo) *vs* placebo after AF ablation (antral PVI and left atrial isthmus ablation). Patients randomized to the colchicine arm had lower levels of inflammatory markers post-ablation (C-reactive protein and IL-6) compared with placebo, and were less likely to experience ERAA within the 3-mo blanking period (16% *vs* 33.5%; OR = 0.38; 95%CI: 0.18-0.8) *vs* placebo. In a larger subsequent study, Deftereos *et al*[45] found that patients randomized to colchicine for 3 mo post-ablation had a significantly lower single-procedure late AF recurrence rate after a median follow-up duration 15 mo (31.1% *vs* 49.5%; OR = 0.46; 95%CI: 0.26-0.81). Colchicine is a relatively benign medication (with its major side-effect being gastrointestinal upset), and the results of these preliminary studies are certainly promising. However, future, larger prospective studies are required to confirm the benefit of colchicine after ablation before it can be widely accepted.

TREATMENT OF ERAA

Timing of cardioversion

In patients experiencing ERAA after AF ablation, early cardioversion might improve long-term ablation success. Restoration of sinus rhythm may prevent AF-induced progression of adverse LA remodeling, thus facilitating maintenance of sinus rhythm. Chilukuri *et al*[46] examined timing to cardioversion (before *vs* after the 3-mo blanking period) in patients with nonparoxysmal AF treated with ablation and reported an extremely low (16%) rate of long-term ablation success in patients treated with early cardioversion for persistent AF/OAT during the blanking period, although the rate of long-term freedom from AF was even more dismal (8%) among those who underwent late cardioversion after the blanking period. Baman *et al*[47] examined the effect of the timing of cardioversion after ERAA in 93 patients treated with antral PVI for AF. They found that time to cardioversion was inversely correlated with long-term freedom from AF off AAD: Those who were cardioverted within 30 d (*vs* those cardioverted after 30 d) of ERAA were more likely to remain in sinus rhythm over the remainder of the study duration (OR = 22.5, 95%CI: 4.87-103.88, $P < 0.0001$). Additionally, time between ERAA and cardioversion was the only independent predictor of sinus rhythm maintenance in their multivariate model.

At our institution we aim to restore sinus rhythm as soon as possible in patients with ERAA since we believe that maintenance of sinus rhythm allows for favorable structural, electrical, and mechanical remodeling of the atria and may maximize the likelihood of achieving long-term ablation success. However, it remains to be determined whether the benefits of this approach are similar between paroxysmal and non-paroxysmal types of AF.

Early reablation

The optimal timing for repeat ablation in patients with ERAA remains unknown. As discussed throughout this review, a number of factors including arrhythmia characteristics, patient characteristics, ablation procedural characteristics, and recurrence characteristics play a role in predicting long-term ablation success. The goal is to identify patients in whom ERAA is not just due to transient post-ablation factors, and in whom ablation early in the recurrence course may be more likely to result in long-term ablation success. In a study by Lellouche *et al*[14], of 302 patients with persistent and paroxysmal AF, they reported their experience of 302 patients with persistent and paroxysmal AF, 151 patients had ERAA, 61 of whom were treated with very early reablation (within 1 mo of the index ablation). They found that patients who underwent early reablation had a significantly lower rate of late recurrences (51% *vs* 91%; $P < 0.0001$), although they required more total procedures over the entire follow-up period (2.5 ± 0.7 *vs* 2.2 ± 0.6; $P = 0.02$). Additionally, Andrade *et al*[7] found that patients with ERAA after cryoablation in the STOP AF trial who underwent early reablation during the blanking period were significantly less likely to have late recurrences out to 1 year follow-up (33% *vs* 56% late recurrence rate; HR = 0.04, 95%CI: 0.01-0.32; $P = 0.002$). While their results suggest that early reablation within the blanking period for ERAA after cryoablation improves long-term ablation success, the authors acknowledge that it is possible that reablation may not have been necessary in all patients since it is possible that ERAA may have resolved spontaneously in some.

Recently, Yanagisawa *et al*[48] performed a retrospective analysis examining outcomes after early reablation during the first 3 months post-ablation in 66 patients with ERAA. Compared to 66 propensity-matched controls who did not undergo early reablation, the patients treated with early reablation had a significantly lower rate of late recurrence (64% *vs* 44%; $P = 0.023$), but required more additional procedures (0.4 *vs* 1.2 procedures; $P = 0.001$). Interestingly, the benefit of early reablation for ERAA was limited to those with paroxysmal AF (37% *vs* 66% late recurrence rate for early reablation *vs* no early reablation; $P = 0.008$), while there was no significant benefit to early reablation in those with persistent AF (56% *vs* 60%; $P = 0.77$). Furthermore, 36% of those with ERAA who did not undergo early reablation had no further recurrences in after the 3-mo blanking period.

We have recently shown that in patients with non-paroxysmal AF treated with a limited ablation strategy of antral PVI and targeting of non-PV triggers, patients who recur as paroxysmal (rather than persistent) AF type are more likely to experience long-term ablation success[49]. We believe that patients with persistent or longstanding persistent AF who experience paroxysmal-type ERAA after ablation may represent a subgroup of patients in whom early reablation (even during the blanking period)

can improve long-term ablation success. Transformation of nonparoxysmal AF to paroxysmal AF may represent favorable alteration of the underlying substrate, and we hypothesize that early intervention before AF is allowed to become persistent again (and cause adverse LA electrical and structural remodeling) might result in improved outcomes.

CONCLUSION

Early recurrences of atrial arrhythmia are common in the post-ablation period, and detection of ERAA is dependent on the monitoring strategy. Although ERAA clearly predicts late AF recurrences, some patients with ERAA do not develop late recurrence and thus the guidelines recommend a 3-mo blanking period during which recurrences should not be considered as ablation failure. However, ERAA episodes which occur later within the blanking period (particularly after the first 2 weeks) as well as multiple ERAA occurrences appear to be strongly predictive of late recurrence. Thus, the optimal blanking period during which ERAA events may be benign remains unclear. While pharmacologic agents such as AADs and corticosteroids reduce the incidence of ERAA, they do not improve long-term ablation success. Colchicine is a promising medication which has been shown in isolated studies to decrease both early and late recurrences but larger prospective studies are necessary to validate this effect. Whether reablation should be performed in patients experiencing ERAA remains undetermined. Further studies are necessary to elucidate the optimal timing for reablation based on patient and ERAA characteristics to maximize long-term ablation success.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical characteristics and prognostic impact of atrial fibrillation in patients with chronic heart failure

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Data sharing statement: Statistical code and dataset are available from the corresponding author at his email address. All data are anonymized and there is no risk of patients' identification.

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Abstract

AIM

To assess the prevalence, clinical characteristics and independent prognostic impact of atrial fibrillation (AF) in chronic heart failure (CHF) patients, and the potential protective effect of disease-modifying medications, particularly beta-blockers (BB).

METHODS

We retrospectively reviewed the charts of patients referred to our center since January 2004, and collected all clinical information available at their first visit. We assessed mortality to the end of June 2015. We compared patients with and without AF, and assessed the association between AF and all-cause mortality by

multivariate Cox regression and Kaplan-Meyer analysis, particularly accounting for ongoing treatment with BB.

RESULTS

A total of 903 patients were evaluated (mean age 68 ± 12 years, 73% male). Prevalence of AF was 19%, ranging from 10% to 28% in patients ⩽ 60 and ⩾ 77 years, respectively. Besides the older age, patients with AF had more symptoms (New York Heart Association II-III 60% *vs* 44%), lower prevalence of dyslipidemia (23% *vs* 37%), coronary artery disease (28% *vs* 52%) and left bundle branch block (9% *vs* 16%). On the contrary, they more frequently presented with an idiopathic etiology (50% *vs* 24%), a history of valve surgery (13% *vs* 4%) and received overall more devices implantation (31% *vs* 21%). The use of disease-modifying medications (*i.e.*, BB and ACE inhibitors/angiotensin receptor blockers) was lower in patients with AF (72% *vs* 80% and 71% *vs* 79%, respectively), who on the contrary were more frequently treated with symptomatic and antiarrhythmic drugs including diuretics (87% *vs* 69%) and digoxin (51% *vs* 11%). At a mean follow-up of about 5 years, all-cause mortality was significantly higher in patients with AF as compared to those in sinus rhythm (SR) (45% *vs* 34%, *P* value < 0.05 for all previous comparisons). However, in a multivariate analysis including the main significant predictors of all-cause mortality, the univariate relationship between AF and death (HR = 1.49, 95%CI: 1.15-1.92) became not statistically significant (HR = 0.98, 95%CI: 0.73-1.32). Nonetheless, patients with AF not receiving BB treatment were found to have the worst prognosis, followed by patients with SR not receiving BB therapy and patients with AF receiving BB therapy, who both had similarly worse survival when compared to patients with SR receiving BB therapy.

CONCLUSION

AF was highly prevalent and associated with older age, worse clinical presentation and underutilization of disease-modifying medications such as BB in a population of elderly patients with CHF. AF had no independent impact on mortality, but the underutilization of BB in this group of patients was associated to a worse long-term prognosis.

Key words: Atrial fibrillation; Chronic heart failure; Beta-blockers; Digoxin; Prognosis

Core tip: In this retrospective analysis atrial fibrillation (AF) was diagnosed in 1 out of 5 patients with chronic heart failure. The arrhythmia was associated with older age, worse clinical presentation and underutilization of disease-modifying medications, particularly beta-blockers (BB) and ACE inhibitors/angiotensin receptor blockers. At a mean follow-up of about 5 years, mortality was significantly higher in patients with AF, and patients with AF not receiving BB treatment were found to have the worst prognosis. However, in a multivariate analysis including main significant predictors of all-cause mortality, such as age, gender, blood pressure, coronary artery disease, comorbidities and medications, the univariate relationship between AF and death became not statistically significant.

Gigli L, Ameri P, Secco G, De Blasi G, Miceli R, Lorenzoni A, Torre F, Chiarella F, Brunelli C, Canepa M. Clinical characteristics and prognostic impact of atrial fibrillation in patients with chronic heart failure. *World J Cardiol* 2016; 8(11): 647-656 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i11/647.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i11.647

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia and frequently coexists with chronic heart failure (CHF)[1]. It is commonly held that CHF decompensated by a transient AF episode has better prognosis than CHF with permanent AF[2]. However, the real prognostic impact of permanent AF in patients with CHF remains poorly understood[3-6] and a matter of current debate[7,8]. Conflicting data also exist on medical treatment of CHF patients with AF, particularly in the elderly. Indeed, although beta-blockers (BB) are a corner-stone therapy of CHF, their value when AF coexists has recently been questioned[9]. Thus, the aim of this study was to investigate the prevalence, clinical characteristics and prognostic impact of permanent AF in a cohort of unselected CHF patients referred to a single tertiary outpatient clinic. In particular, we assessed whether a diagnosis of permanent AF was independently associated with increased all-cause mortality, and whether this association was influenced by medical therapy with BB.

MATERIALS AND METHODS

Study population

The study population was drawn from a tertiary CHF outpatient clinic; all patients with a diagnosis of CHF, New York Heart Association (NYHA) functional class between I and III and a readable rest ECG were considered eligible. Data were retrospectively collected by reviewing all available complete records of the first visit at the clinic between January 1st 2004 and May 31st 2015. A total of 941 unique patients were originally included; 23 patients were subsequently excluded because they did not have a readable ECG, and another 10 patients because the heart rhythm was not clearly definable due to pacemaker stimulation. Mortality was ascertained by consulting hospital and administrative databases and death registers. Follow-up was censored at June 30, 2015; survival status was not retrievable

in five patients, leaving a final study sample of 903 patients.

All patients signed an informed consent allowing the utilization of their anonymized clinical information for medical research purposes, as approved by the local Institutional Review Board.

Variables of interest

Permanent AF (subsequently indicated solely as AF) was defined as a documented history of AF that had persisted for more than 6 mo and was confirmed by a surface ECG at first visit. A diagnosis of coronary artery disease (CAD) was ascertained by coronary angiography, and patients without any luminal stenosis > 50% were considered without CAD. Information regarding previous percutaneous and/or surgical revascularization and previous valve surgery was also routinely collected. The remaining patients with other CHF etiology (including hypertensive cardiac disease, valve disease, tachycardiomyopathy, idiopathic cardiomyopathy) were all incorporated in a single group. Implanted devices were divided as follows: Mono/bicameral pacemakers (PM), biventricular pacemakers (CRT-D/CRT-P) and implantable-cardioverter defibrillators (ICD). Hypertension was defined by a blood pressure $\geqslant$ 140/90 and/or the use of antihypertensive medications. Diabetes mellitus was defined by history of diabetes mellitus and/or a random plasma glucose $\geqslant$ 200 mg/dL and/or fasting plasma glucose $\geqslant$ 126 mg/dL and/or an HbA1c $\geqslant$ 7% and/or use of antidiabetic treatments. Dyslipidemia was defined by history of high cholesterol levels and/or a total cholesterol $\geqslant$ 200 mg/dL. Present or former smoking was ascertained by medical interview, and patients who had smoked > 100 cigarettes/year were considered as smoker. Cancer history was defined by a previous or current malignancy, regardless of disease status at the time of medical interview. A clinical diagnosis of chronic obstructive pulmonary disease (COPD) was made during the visit based on the presence of a history of COPD, and/or signs and/or symptoms suggestive of COPD including chronic productive cough, chronic wheezing, emphysema or bronchitis.

Lab tests completed within 3 mo from the study visit were considered to identify anemia (hemoglobin levels < 13.5 g/dL in male and < 12.5 g/dL in female patients) and chronic kidney disease (CKD: Estimated glomerular filtration rate < 60 mL/min per 1.73 m^2 as calculated from creatinine using the CKD-EPI formula).

The following variables were collected from a basal 12-lead standard ECG: Heart rhythm, heart rate, and presence of a right or left bundle branch block. Left ventricular ejection fraction (LVEF) was derived from a transthoracic echocardiogram obtained within 3 mo from the first visit, and patients with a LVEF > 45% were considered as having a preserved LVEF.

Information regarding ongoing medications was ascertained for each patient, and included CHF-modifying drugs [*i.e.*, BB, ACE inhibitors and/or angiotensin receptor antagonists (ACEi/ARB) and aldosterone antagonists], diuretics (both loop diuretics and thiazides), other blood pressure lowering drugs (such as calcium channel blockers and alpha blockers), digoxin, amiodarone, lipid-lowering drugs (*i.e.*, statins) antiplatelet drugs (including aspirin, clopidogrel and - for very few patients - ticagrelor), and anticoagulants (*i.e.*, warfarin and very few patients with direct factor X or thrombin inhibitors).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as percentages. Characteristics of patients with AF *vs* sinus rhythm (SR) were compared using student's *t* test and χ^2 test as appropriate. To define univariate predictors of all-cause mortality, we compared characteristics of dead *vs* alive patients at the end of follow-up. Univariate and multivariate predictors of mortality were also investigated by Cox regression analysis. Variables with a *P* value < 0.10 in univariate analysis were selected based on clinical and statistical criteria (*i.e.*, to ease the interpretation of the analysis and to avoid multicollinearity) and introduced into a multivariate model. A backward elimination of variables with a *P* value > 0.05 was performed to obtain the final multivariate reduced model. Kaplan-Meyer curves were obtained for all-cause mortality in patients with AF *vs* SR, and also based on the use of BB medications. All analyses were performed using SAS for Windows (version 9.2; SAS Institute Inc, Cary, NC). The statistical review of the manuscript was performed by a biomedical statistician.

RESULTS

Study population

From January 2004 to May 2015, a total of 903 patients were evaluated who satisfied our inclusion criteria (mean age 68 ± 12 years, 73% male). Prevalence of AF was 19%, ranging from 10% to 28% in patients $\leqslant$ 60 and $\geqslant$ 77 years of age, respectively (*P* < 0.0001). Characteristics of study population by the presence of AF or SR are summarized in Table 1. Patients with AF were significantly more symptomatic in comparison to patients with SR (NYHA class Ⅱ-Ⅲ 60% *vs* 44%). CAD was less common in patients with AF than in those with SR (28% *vs* 52%), as were previous coronary revascularization (21% *vs* 37%) and dyslipidemia (23% *vs* 37%). By contrast, a non-ischemic etiology was more frequent in the AF group (50% *vs* 24%), as well as a history of previous valve surgery (13% *vs* 4%). Patients with AF received overall more devices implantation (31% *vs* 21%). ECG data showed a lower prevalence of left bundle branch block (9% *vs* 16%) and a higher mean heart rate (80 ± 19 *vs* 70 ± 13) in patients with AF. Patients with AF were more frequently diagnosed with CHF with preserved LVEF (29% *vs* 21%).

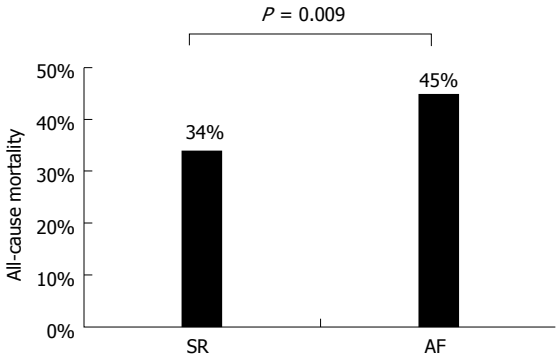

Figure 1 All-cause mortality in patients with atrial fibrillation and in patients with sinus rhythm. SR: Sinus rhythm; AF: Atrial fibrillation.

Treatment differences in patients with AF

When AF was present, there was a significant lower percentage of treatment with disease-modifying medications, including BB (72% *vs* 80%) and ACEi/ARB (51% *vs* 66%), as well as a less frequent use of calcium channel blockers (6% *vs* 13%), statins (28% *vs* 49%), amiodarone (6% *vs* 13%) and antithrombotic treatment (19% *vs* 63%). On the contrary, treatment with diuretics (87% *vs* 69%), aldosterone blockers (46% *vs* 37%), digoxin (87% *vs* 69%) and oral anticoagulants (82% *vs* 16%) was lower in patients with SR (Table 1).

Mortality in the study population

At a mean follow-up of 59 ± 40 mo (range 1 to 137 mo), all-cause mortality was significantly higher in patients with AF as compared to those in SR (45% *vs* 34%, Figure 1). Patients with AF were more likely to die during the course of our extended follow-up (Figure 2). Table 2 shows univariate associations of variables listed in Table 1 with all-cause mortality. At univariate analysis, patients who died had more frequently a diagnosis of AF than those who survived (23% *vs* 16%), were significantly older at baseline (71 ± 10 years *vs* 66 ± 12 years), had lower systolic and diastolic blood pressure (127 ± 19 mmHg *vs* 130 ± 19 mmHg, 72 ± 10 mmHg *vs* 76 ± 10 mmHg, respectively) and had more often NYHA class II-III (60% *vs* 40%), idiopathic etiology of CHF (32% *vs* 26%), implantable devices (29% *vs* 19%), PM stimulation (14% *vs* 9%) and a history of ventricular tachycardia (7% *vs* 4%). Moreover, diabetes mellitus (32% *vs* 24%), cancer history (14% *vs* 8%), COPD (18% *vs* 10%), chronic anemia (11% *vs* 8%), CKD (10% *vs* 6%), and use of diuretics (82% *vs* 67%), digoxin (26% *vs* 14%) or aldosterone blockers (45% *vs* 35%) was more frequent in the group of patients who died at follow-up. On the contrary, variables associated with survival were the presence of dyslipidemia (27% *vs* 39%), a preserved LVEF (19% *vs* 24%), and the use of BB (72% *vs* 82%) and ACEi/ARB (75% *vs* 79%) (Table 2).

In a multivariate analysis including the main significant predictors of all-cause mortality, the univariate relationship between AF and death (HR = 1.49, 95%CI: 1.15-1.92) became not statistically significant (HR =

Table 1 Characteristics of study population by presence of atrial fibrillation or sinus rhythm at baseline

	Atrial fibrillation (*n* = 173)	Sinus rhythm (*n* = 730)	*P* value
Demographics and physical examination			
Age (yr)	72 ± 11	66 ± 12	< 0.0001
Age ⩾ 65 yr (%)	81	60	< 0.0001
Male gender (%)	70	73	0.42
SBP (mmHg)	127 ± 18	130 ± 19	0.10
DBP (mmHg)	74 ± 10	75 ± 10	0.47
NYHA II-III (%)	60	44	0.0002
Aetiology			
CAD (%)	28	52	< 0.0001
Previous CABG/PCI (%)	21	37	< 0.0001
Without CAD (%)	22	24	0.58
Others/idiopathic (%)	50	24	< 0.0001
Valve surgery (%)	13	4	< 0.0001
Device			
Any PM (%)	30	19	0.001
CRT-P/CRT-D (%)	10	7	0.14
ICD (%)	11	16	0.07
Any device (%)	31	21	0.005
History of VT (%)	2	5	0.06
Risk factors			
Hypertension (%)	61	60	0.81
Diabetes mellitus (%)	24	28	0.39
Dyslipidaemia (%)	23	37	0.0004
Ever smoke (%)	27	41	0.0010
Comorbidities			
Cancer history (%)	12	10	0.47
COPD (%)	14	13	0.55
Anaemia (%)	6	10	0.11
CKD (eGFR < 60) (%)	7	8	0.57
ECG			
Heart rate (bpm)	80 ± 19	70 ± 13	< 0.0001
PM stimulation (%)	24	8	< 0.0001
Right bundle branch block (%)	7	5	0.65
Left bundle branch block (%)	9	16	0.01
Echocardiogram			
Preserved LVEF (> 45%) (%)	29	21	0.022
LVEF (%)	38 ± 14	35 ± 12	0.05
Medications			
Beta-blockers (%)	72	80	0.01
ACEi/ARB (%)	71	79	0.02
Beta-blockers and ACEi/ARB (%)	51	66	0.0003
Aldosterone blockers (%)	46	37	0.02
Diuretics (%)	87	69	< 0.0001
Calcium channel blockers (%)	6	13	0.01
Alfa-blockers (%)	6	8	0.55
Digoxin (%)	51	11	< 0.0001
Statin (%)	28	49	< 0.0001
Amiodarone (%)	6	13	0.01
Antithrombotic treatment (%)	19	63	< 0.0001
OAT (%)	82	16	< 0.0001
DAPT (%)	2	16	< 0.0001
OAT and antithrombotic (%)	8	2	0.0006
Antithrombotic only (%)	11	61	< 0.0001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NYHA: New York Heart Association; CAD: Coronary artery disease; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; PM: Pacemaker; CRT-P/D: Cardiac resynchronization therapy pacing/defibrillator; ICD: Internal cardioverter defibrillator; VT: Ventricular tachycardia; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate (obtained by CKD-EPI formula); LVEF: Left ventricular ejection fraction; ACEi: ACE inhibitors; ARB: Angiotensin receptor blockers; OAT: Oral anticoagulant treatment; DAPT: Dual anti-platelet therapy.

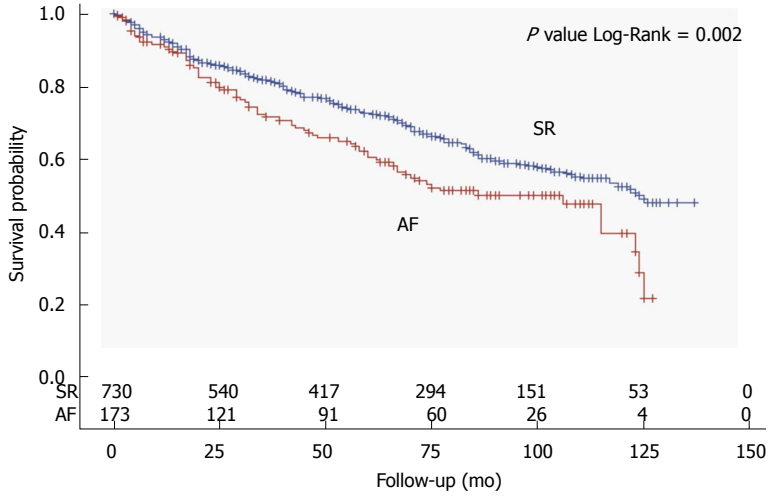

Figure 2 Kaplan-Meier curves of overall survival according to the presence of atrial fibrillation or sinus rhythm. SR: Sinus rhythm; AF: Atrial fibrillation.

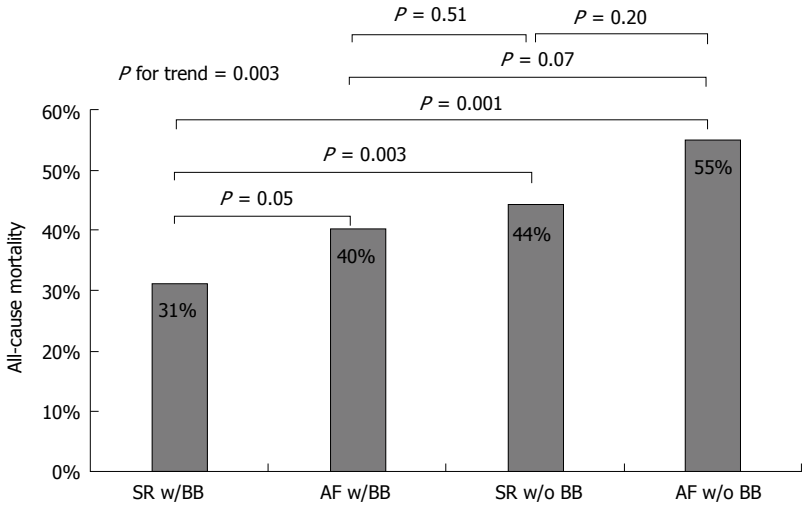

Figure 3 All-cause mortality in patients with atrial fibrillation as compared to patients with sinus rhythm based on the use of beta-blocker medications. SR: Sinus rhythm; AF: Atrial fibrillation; BB: Beta-blocker.

0.98, 95%CI: 0.73-1.32, Table 3). In the final reduced multivariate model, independent predictors at baseline of all-cause mortality were the following: Older age, male gender, lower systolic blood pressure, NYHA class II-III, presence of CAD at coronary angiography, presence of an implanted device, diagnosis of diabetes mellitus, COPD or anemia, history of cancer, non-use of ACEi/ARB and statins, and use of diuretics and digoxin (Table 3).

Mortality differences by BB medications

All-cause mortality was studied also through a comparison between patients with SR and patients with AF based on the presence or absence of BB treatment. Patients with AF not receiving BB treatment were found to have the worst prognosis, followed by patients with SR not receiving BB therapy and patients with AF receiving BB therapy, who both had similarly worse survival when compared to patients with SR receiving BB therapy (Figure 3). During the course of follow-up, patients with AF not receiving BB treatment had the worst prognosis, followed by patients with SR not receiving BB therapy together with patients with AF receiving BB therapy, and finally patients with SR receiving BB therapy (Figure 4).

DISCUSSION

Overall, our data demonstrates that in ambulatory patients with CHF, the presence of permanent AF is associated with worse clinical presentation, underuse of disease-modifying medications including BB, and possibly worse prognosis. After accounting for confounders, we found no independent association between AF and all-cause mortality; nonetheless, we found a significantly worse prognosis in AF patients with CHF not receiving BB treatment.

Patients with AF in our study population were older and had a higher NYHA functional class at presentation, in agreement with other data reported in the litera-

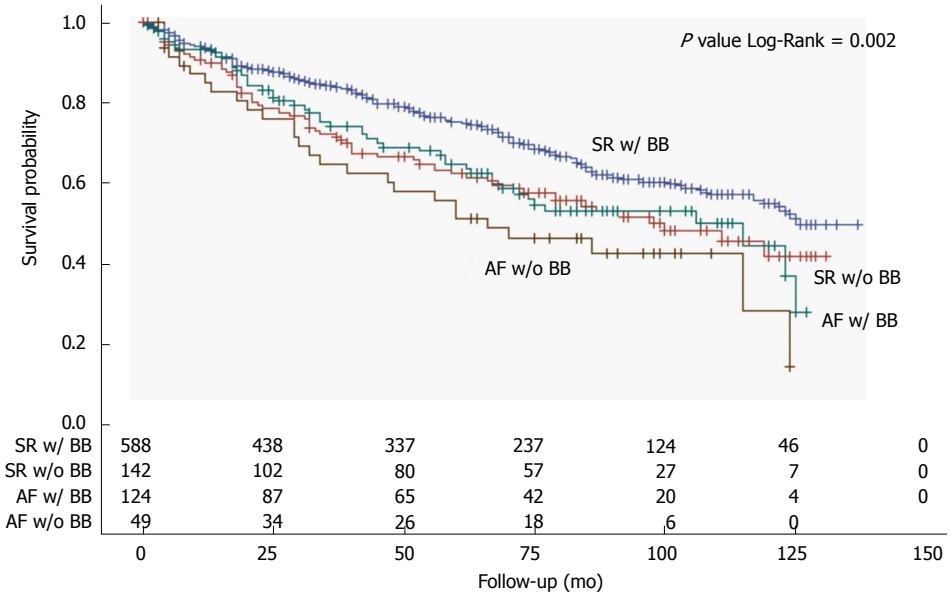

Figure 4 Kaplan-Meier curves of overall survival according to the presence of atrial fibrillation or sinus rhythm and the use of beta-blocker medications. SR: Sinus rhythm; AF: Atrial fibrillation; BB: Beta-blocker.

Table 2 Characteristics of study population by survival or death

	Death (n = 324)	Alive (n = 579)	P value	HR (95%CI)	P value
Atrial fibrillation (%)	23	16	0.0085	1.48 (1.14-1.92)	0.0028
Demographics and physical examination					
Age (yr)	71 ± 10	66 ± 12	< 0.0001	1.05 (1.04-1.06)	< 0.0001
Male gender (%)	25	29	< 0.0001	2.4 (1.85-3.07)	< 0.0001
SBP (mmHg, 10)	127 ± 19	130 ± 19	0.0238	0.93 (0.88-0.99)	0.0228
DBP (mmHg, 10)	72 ± 10	76 ± 10	< 0.0001	0.76 (0.67-0.85)	< 0.0001
NYHA II-III (%)	60	40	< 0.0001	1.7 (1.35-2.10)	< 0.0001
Aetiology					
CAD (%)	51	46	0.18		
Previous CABG/PCI (%)	33	35	0.57		
Without CAD (%)	17	27	0.0002	0.53 (0.4-0.71)	< 0.0001
Others/idiopathic	32	26	0.049	1.29 (1.02-1.63)	0.0302
Valve surgery (%)	5	6	0.57		
Device					
Any PM (%)	28	17	0.0003	1.64 (1.29-2.1)	< 0.0001
CRT-P/CRT-D (%)	8	7	0.32		
ICD (%)	20	13	0.0027	1.45 (1.1-1.9)	0.0074
Any device (%)	29	19	0.0006	1.57 (1.23-2.00)	0.0002
History of VT (%)	7	4	0.0258	1.53 (1.01-2.32)	0.0439
Risk factors					
Hypertension (%)	58	61	0.2619		
Diabetes mellitus (%)	32	24	0.0053	1.72 (1.36-2.17)	< 0.0001
Dyslipidaemia (%)	27	39	0.0003	0.68 (0.53-0.87)	0.0023
Ever smoke (%)	32	41	0.0055	0.92 (0.72-1.16)	0.4668
Comorbidities					
Cancer history (%)	14	8	0.0044	1.89 (1.37-2.60)	< 0.0001
COPD (%)	18	10	0.0006	1.84 (1.4-2.40)	< 0.0001
Anaemia (%)	11	8	0.0521	2.22 (1.57-3.13)	< 0.0001
CKD (eGFR < 60) (%)	10	6	0.0551	2.807 (1.85-4.25)	< 0.0001
ECG					
Heart rate (bpm, 10)	72 ± 15	70 ± 15	0.1026	1.06 (0.99-1.14)	0.0805
PM stimulation (%)	14	9	0.0438	1.56 (1.14-2.14)	0.0057
Right bundle branch block (%)	7	5	0.0866	1.38 (0.9-2.1)	0.1321
Left bundle branch block (%)	12	16	0.0761	0.75 (0.53-1.05)	0.0958
Echocardiogram					
Preserved LVEF (> 45%) (%)	19	24	0.0560	0.74 (0.56-0.98)	0.0345
LVEF (%)	34 ± 12	36 ± 11	0.0015	0.98 (0.97-0.99)	0.0008
Medications					
Beta-blockers (%)	72	82	0.0003	0.67 (0.53-0.85)	0.0012
ACEi/ARB (%)	75	79	0.0994	0.69 (0.53-0.88)	0.0032

Beta-blockers and ACEi/ARB (%)	32	68	0.003	0.66 (0.53-0.83)	0.0002
Aldosterone blockers (%)	45	35	0.0033	1.57 (1.26-1.95)	< 0.0001
Diuretics (%)	82	67	< 0.0001	2.50 (1.87-3.31)	< 0.0001
Calcium channel blockers (%)	14	11	0.1588		
Alfa-blockers (%)	8	7	0.8049		
Digoxin (%)	26	14	< 0.0001	1.60 (1.25-2.05)	0.0002
Statin (%)	39	48	0.0088	0.80 (0.64-1.00)	0.0513
Amiodarone (%)	12	12	0.8421		
Antithrombotic treatment (%)	56	54	0.5669		
OAT (%)	31	27	0.2374		
DAPT (%)	10	15	0.0282	0.89 (0.62-1.29)	0.5394
OAT and antithrombotic (%)	3	4	0.4946		
Antithrombotic only (%)	53	50	0.4149		

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NYHA: New York Heart Association; CAD: Coronary artery disease; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; PM: Pacemaker; CRT-P/D: Cardiac resynchronization therapy pacing/defibrillator; ICD: Internal cardioverter defibrillator; VT: Ventricular tachycardia; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate (obtained by CKD-EPI formula); LVEF: Left ventricular ejection fraction; ACEi: ACE inhibitors; ARB: Angiotensin receptor blockers; OAT: Oral anticoagulant treatment; DAPT: Dual anti-platelet therapy.

Table 3 Univariate and multivariate predictors of all-cause mortality

	Univariate		Multivariate full		Multivariate reduced	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Atrial fibrillation	1.48 (1.14-1.92)	0.0028	0.98 (0.73-1.32)	0.8896		
Age (1 yr)	1.05 (1.04-1.06)	< 0.0001	1.04 (1.03-1.05)	< 0.0001	1.04 (1.03-1.05)	< 0.0001
Male gender	2.4 (1.85-3.07)	< 0.0001	1.45 (1.11-1.90)	0.0068	1.48 (1.13-1.93)	0.0045
SBP (10 mmHg)	0.93 (0.88-0.99)	0.0228	0.92 (0.86-0.98)	0.0084	0.91 (0.86-0.97)	0.0057
NYHA II-III	1.70 (1.35-2.10)	< 0.0001	1.3 (1.03-1.65)	0.0265	1.32 (1.05-1.66)	0.0195
Without CAD	0.53 (0.4-0.71)	< 0.0001	0.61 (0.44-0.84)	0.0023	0.58 (0.43-0.80)	0.0008
Any device	1.57 (1.23-2.00)	0.0002	1.65 (1.19-2.29)	0.0028	1.57 (1.23-2.02)	0.0004
Dyslipidaemia	0.68 (0.53-0.87)	0.002	0.8 (0.60-1.06)	0.1151		
Diabetes mellitus	1.72 (1.36-2.17)	< 0.0001	1.63 (1.27-2.08)	0.0001	1.59 (1.25-2.04)	0.0002
Cancer history	1.89 (1.37-2.60)	< 0.0001	1.82 (1.31-2.54)	0.0004	1.84 (1.33-2.56)	0.0003
COPD	1.84 (1.4-2.4)	< 0.0001	1.33 (0.98-1.80)	0.0707	1.38 (1.02-1.86)	0.0359
Anaemia	2.22 (1.57-3.13)	< 0.0001	1.82 (1.23-2.69)	0.0027	1.95 (1.37-2.79)	0.0002
CKD (eGFR < 60)	2.81 (1.85-4.25)	< 0.0001	1.42 (0.87-2.29)	0.1577		
Preserved LVEF (> 45%)	0.74 (0.56-0.98)	0.034	0.91 (0.68-1.22)	0.5369		
PM stimulation	1.56 (1.14-2.14)	0.006	0.91 (0.59-1.40)	0.6561		
Beta-blockers	0.67 (0.53-0.85)	0.001	0.83 (0.64-1.09)	0.1903		
ACEi/ARB	0.69 (0.53-0.88)	0.003	0.77 (0.59-1.01)	0.0634	0.73 (0.56-0.94)	0.0169
Aldosterone blockers	1.57 (1.26-1.95)	< 0.0001	1.11 (0.86-1.43)	0.429		
Diuretics	2.5 (1.87-3.31)	< 0.0001	1.51 (1.09-2.10)	0.0134	1.58 (1.17-2.15)	0.0031
Digoxin	1.6 (1.25-2.05)	0.0002	1.29 (0.97-1.73)	0.0807	1.31 (1.00-1.72)	0.0482
Statin	0.8 (0.64-1.00)	0.051	0.8 (0.60-1.05)	0.1108	0.71 (0.55-0.90)	0.0057

Any device included any pacemaker or internal-cardioverter defibrillator. SBP: Systolic blood pressure; NYHA: New York Heart Association; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate by CKD-EPI formula; LVEF: Left ventricular ejection fraction; PM: Pacemaker; ACEi: ACE inhibitors; ARB: Angiotensin receptor blocker.

ture[10,11]. The presence of AF was also associated with an increased use of symptomatic medications, such as diuretics and digoxin, and a less frequent use of CHF-modifying medications, such as BB and ACEi/ARB. In addition, CAD was less represented among AF patients, whereas the prevalence of valve disease and non-cardiovascular comorbidities was greater in this group of patients, who interestingly also had a higher mean LVEF and more frequently a preserved LVEF (here LVEF > 45%). Recent literature emphasizes the stronger correlation of AF with CHF with preserved LVEF as compared to reduced LVEF[12], though this association was rather weak in our population, possibly because it mainly included CHF patients with reduced LVEF. CHF patients with AF are usually characterized by the presence of multiple comorbidities, and it is still unknown whether the adverse outcomes associated with AF are related to the arrhythmia itself, or to the burden of comorbidities associated with this diagnosis[8].

Contrasting findings have been published regarding a potential independent contribution of AF to increased mortality in patients with CHF. Some studies found AF to be an independent predictor of worse outcomes[13,14] whereas others found no independent association after accounting for confounders[4-6]. Two meta-analyses reported a 30%-40% increased risk of mortality when CHF is associated with a diagnosis of AF[7,8], irrespective of LVEF. In our study population, the coexistence of CHF and permanent AF resulted in a worse outcome, as shown by the Kaplan-Meyer survival curve in

Figure 2. However, after adjusting for other significant predictors (including older age, male sex, systolic blood pressure, NYHA class Ⅱ-Ⅲ, ischemic etiology, pacemaker implanted, diabetes mellitus, history of cancer, COPD, anemia), AF did not show an independent impact on overall mortality (Table 3). This finding is in accordance with the abovementioned analyses from the COMET[5] and the V-HeFT study[4]. Advanced age and CHF severity have been shown to largely explain the association between AF and mortality in CHF patients, and this was also true in our study population, in which beyond age and NYHA functional class, we demonstrated a significant and independent contribution of non-cardiovascular comorbidities to mortality, including COPD, anemia and a history of cancer.

Although the use of BB in the setting of CHF has recently been disputed[9], we observed the worst prognosis in AF patients not receiving BB medications, while patients with AF receiving BB presented a significant survival benefit similar to those with SR not receiving BB but still lower than those with SR receiving BB treatment (Figures 3 and 4). It is still uncertain whether BB therapy reduces morbidity and mortality in patients with AF, but a class IA indication is given for these medications in patients with CHF and AF to control ventricular rate[15]. Our present results support this recommendation and point against the underuse of BB medications that is generally observed in CHF with AF as compared to those with SR[9].

The contribution of treatment with digoxin to the worse outcome in patients with CHF and AF is a matter of current debate[16]. We observed that digoxin was used in half of our patients with AF, and in only 1 out of 10 patients with SR. These percentages refer to the use of digoxin at first study visit, which happened some years ago starting in 2004, and probably do not reflect the current use of this medication in our clinical practice. Trends in the use of digoxin for AF have been steadily decreasing in the recent years, at least in the American population[17], and this drug has class IIa/B recommendations for rate control treatment of AF in most recent European[15] and American[18] HF guidelines. This is because of an overall neutral effect of this drug on mortality[19], and some observational studies showing an independent association with increased mortality[20]. Accordingly, its utilization was a strong and independent predictor of mortality at multivariate analysis in our retrospective analysis (Table 3).

The presence of implantable devices was associated with increased mortality in our final multivariate model. This finding appears counterintuitive at first, but may have different explanations. In particular, the presence of a device may be representative of a sicker CHF patient, for which the implantation of a device is generally indicated. In addition, when we distinguished patients with only pacing devices from patients with a resynchronizing device (either CRT-P or CRT-D) and patients with an ICD, only patients with a pacing device and an ICD implanted showed a statistically significant worse prognosis (Table 2). Treatment of LV dyssychrony with CRT device is expected to improve EF and symptoms over time, which in turn has a major positive impact on outcomes, including survival[15]. This is also at least partially reflected by the positive prognostic association of the presence of a left bundle branch block that we found in our study population (Table 2), which is likely indicative of the effect of CRT in patients that were implanted with a resynchronizing device after the first study visit at our clinic.

In contrast to what would be expected, dyslipidemia was associated with a reduction of mortality. In the setting of CHF, the presence of low cholesterol levels is known to identify patients with more advanced cardiac disease (*i.e.*, with sarcopenia and possibly cachexia), and low concentrations of low-density lipoproteins have been associated with worse prognosis[15]. Patients with advanced cardiac disease are also less likely to receive lipid-lowering medications such as statins, for which the indication in CHF patients without active CAD is lacking[15]. Thus, the presence of dyslipidemia and the use of statins in our CHF population of advanced age probably indicate a healthier patient, which explain the associations of both these variables with a better prognosis.

Our analysis has several limitations that should be acknowledged. First, this is a retrospective analysis, thus our findings can only be interpreted with the intrinsic limits of this methodology. Second, cardiac rhythm was defined at first study visit, and we cannot exclude subsequent rhythm modifications. Third, we assessed mortality from all causes and could not obtain clear information specifically on cardiovascular and non-cardiovascular mortality. Because a history of cancer was a significant predictor of increased mortality, in an attempt to remove deaths due to malignancy, we performed sensitivity analysis excluding patients with a positive history of cancer. This analysis included 812 patients, of whom 659 with SR (81%) and 153 with AF (19%), and a total of 279 deaths out of the original 324. In this subsample, final results of independent predictors of mortality were substantially unchanged (data not shown). Finally, due to the low number of patients with preserved LVEF, we could not explore the interaction between LVEF and AF on mortality.

Our retrospective cohort study investigating a real-world population of elderly ambulatory CHF patients confirmed the association of AF with older age and worse clinical presentation previously reported in the literature. It further highlighted how a diagnosis of AF also led to an underutilization of disease-modifying medications such as BB and ACEi/ARBs, and to a more frequent use of symptomatic and antiarrhythmic drugs, particularly diuretics and digoxin, which in turn were independently associated with worse prognosis. In multivariate analysis, AF had no independent impact on all-cause mortality, which nonetheless was found to be the highest in AF patients not receiving BB medications. Further prospective randomized studies are needed

investigating the independent prognostic impact of BB treatment in CHF with AF.

COMMENTS

Background

Atrial fibrillation (AF) frequently coexists with chronic heart failure (CHF). Conflicting data exist on the prevalence, clinical characteristics and medical treatment of HF patients with AF, particularly in the elderly. The independent prognostic impact of AF in these patients also remains unknown, as well as the potential protective effect of disease-modifying medications, particularly beta-blockers (BB).

Research frontiers

The independent prognostic impact of AF in patients with CHF is a current matter of debate, and many have argued that this association is solely explained by other conditions associated to this arrhythmia, particularly comorbidities and underuse of disease-modifying medications.

Innovations and breakthroughs

This analysis confirmed the relevant clinical impact of AF in patients with CHF, although like other previous studies in the literature found no independent prognostic impact of this arrhythmia on overall mortality at long-term follow-up after accounting for several important confounders which are frequently found in these elderly CHF patients.

Applications

The study findings highlight the underuse of disease-modifying medications in CHF patients with coexisting AF, particularly BB. This is a matter of current debate in the clinical arena, with international guidelines giving a strong recommendation for the use of BB as a first-line treatment to control ventricular rate in euvolemic patients with New York Heart Association class I-III CHF. Efforts need to be done in order to increase the appropriate use of these medications in CHF with AF in the real world.

Peer-review

This interesting study by Gigli *et al* examined the impact of AF on outcomes in patients with CHF. The authors conclude that AF did not have an independent impact on mortality, but BB use appeared to affect this relationship.

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ORIGINAL ARTICLE

Observational Study

Riata silicone defibrillation lead with normal electrical measures at routine ambulatory check: The role of high-voltage shock testing

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Author contributions: De Maria E contributed to concept design, data analysis/interpretation, drafting the article, critical revision, approval, statistics and data collection; Borghi A, Bonetti L, Fontana PL, Cappelli S contributed to drafting the article, critical revision, approval, statistics and data collection.

Institutional review board statement: The study was approved by the Institutional Board of our Department (Ethical Committee of Modena Province, Italy).

Informed consent statement: Patient's consent was obtained.

Conflict-of-interest statement: The authors report no relationships that could be construed as a conflict of interest.

Data sharing statement: Technical appendix, statistical code, dataset available from the corresponding author at e.demaria@inwind.it.

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Abstract

AIM

To describe our experience with shock testing for the evaluation of patients with Riata™ leads.

METHODS

Among 51 patients with normal baseline electrical parameters, 20 died during follow-up. Of the remaining 31 patients, 15 underwent the test: In 10 cases a defibrillation testing with ventricular fibrillation (VF) induction and in 5 cases a R-wave-synchronized shock (> 20 J, without inducing VF). The test was performed under sedation with Midazolam.

RESULTS

Twelve patients (80%) had a normal behavior during shock testing: In 8 cases induced VF was correctly detected and treated; in 4 cases of R-wave-synchronized shock electrical parameters remained stable and normal. Three patients (20%) failed the test. One patient with externalized conductors showed a sudden drop of high-voltage impedance (< 10 Ohm) after a 25 J R-wave-synchronized shock. Two other patients with externalized conductors, undergoing defibrillation testing, showed a short-circuit during shock delivery and the implantable cardioverter defibrillator was unable to interrupt VF.

CONCLUSION

In Riata™ leads the delivery of a low current during

routine measurement of high-voltage impedance may not reveal a small short circuit, that can only be evident by attempting to deliver a true shock, either for spontaneous arrhythmias or in the context of a shock testing.

Key words: Implantable cardioverter defibrillator; Lead failure; Defibrillation testing; Riata™ lead; Externalized conductors

Core tip: The management of Riata™ defibrillator leads is complex and optimal treatment is often carried out on individual basis. These leads are prone to a unique failure mechanism: The conductors can externalize through the silicone insulation ("inside-out" abrasion) and appear outside the lead body leading to electrical failure. The potential role of high-voltage shock testing for these leads has been poorly studied, only sparse reports being available. In Riata™ leads the delivery of a low current during routine measurement of high-voltage impedance may not reveal a small short circuit, that can only be evident by attempting to deliver a true shock, either for spontaneous arrhythmias or in the context of a shock testing. Defibrillation testing (or alternatively synchronized shock) should be considered an important tool to check Riata™ integrity.

De Maria E, Borghi A, Bonetti L, Fontana PL, Cappelli S. Riata silicone defibrillation lead with normal electrical measures at routine ambulatory check: The role of high-voltage shock testing. *World J Cardiol* 2016; 8(11): 657-666 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i11/657.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i11.657

INTRODUCTION

The Riata™ St. Jude Medical family of implantable cardioverter defibrillator (ICD) silicone leads underwent class I recall by the Food and Drug Administration in December 2011. These leads are prone to a unique failure mechanism: The conductor cables can externalize through the silicone insulation ("inside-out" abrasion) and appear outside the lead body[1]. The prevalence of externalized conductors (EC) is lower in 7Fr compared to 8Fr leads (9.3% *vs* 24.2%)[2]. The rate of electrical failure can be > 6% per year[3] and it is not always associated with EC[2,4,5]. However, a meta-analysis of 23 observational studies showed that the presence of EC increased the risk of electrical failure by more than 6-fold[6].

The management of patients with Riata™ leads is complex and optimal treatment is often carried out on individual basis. The most important factors to consider are: presence of electrical abnormalities; presence and degree of EC; patient's characteristics. When EC is discovered in absence of electrical abnormalities an "opportunistic" approach is suggested based on patient's risk profile and lead's characteristics[4,5]. The Food and Drug Administration, the manufacturer and many scientific societies do not recommend preemptive routine replacement/removal of externalized functional leads. Riata lead extraction is difficult (especially with EC) so it is not a first choice when the lead seems to function normally[5,7]. However essential questions arise: Will the system defibrillate the heart? Can we rely on a lead with normal electrical parameters even when EC is not evident?

In this paper we retrospectively describe our experience with high-voltage (HV) shock testing for the evaluation of Riata™ leads with normal baseline electrical parameters, with and without EC. We also review current scientific evidence and potential role of HV shock testing (full defibrillation testing or commanded R-wave-synchronized shock).

MATERIALS AND METHODS

Overview of Riata leads in our center

From 2003 to 2010 we implanted 60 Riata™ silicone leads: 51 8Fr (85%), 57 dual-coil (95%). Starting from 2012 we initiated a follow-up program according to manufacturer and Italian Arrhythmological Society (AIAC) recommendations, with fluoroscopic evaluation in three orthogonal views (PA: Postero-anterior; LAO/RAO: Left and right anterior oblique - 40°) at least once a year. Externalized conductors were found in 22% of cases (same percentage in 8Fr and 7Fr). Electrical abnormalities were found in 9 patients (15%): Two failed defibrillation testing (DFT) (two patients described afterward), electrical noise by non-physiological signals (n = 3), significant increase in pacing threshold (n = 2), decrease in R-wave amplitude (n = 1), drop of HV impedance after shock (n = 1). Notably in 3-out-9 cases electrical dysfunction occurred in absence of externalization (electrical noise in two cases, increase in pacing threshold in the other). Electrical abnormalities without EC occurred all with 8Fr dual-coil leads. All patients with electrical dysfunction were advised to have the lead extracted or replaced. Patients with normal electrical parameters (with or without EC) were evaluated in our ambulatory every 3-6 mo.

Defibrillation testing and R-wave-synchronized shock testing

Among 51 patients without baseline electrical dysfunction, 20 died during the follow-up period (3 cases of sudden unexplained death, before 2010, not further investigated). From 2014 we started to consider a HV shock testing in selected cases: At the time of generator replacement, in high risk patients or high risk leads (Table 1). Of the remaining 31 patients with normal baseline electrical parameters, 15 underwent the test: In 10 cases a DFT [ventricular fibrillation (VF) induction with shock-on-T or DC Fibber™] and in 5 cases a R-wave-synchronized shock (> 20 J,

Table 1 Potential role of high-voltage shock testing for the management of Riata™ leads with normal baseline electrical measures

At the time of generator replacement
All cases, with and without externalization, except if contraindications
Independently of generator replacement (case-by-case evaluation)
High risk patient: Recent/prior appropriate ICD shocks; secondary prevention; pacemaker dependency; young age
High risk lead: Externalization, especially if worsening over time; minimal change in electrical parameters not sufficient to define malfunction; 8Fr dual coil leads (?); 1570-1580-1590 families (?)
When to perform: Within 6-12 mo of an effective shock?
How often: Each 6-12 mo?
Contraindication or excessive risk with ventricular fibrillation induction
Commanded synchronized HV shock (preferably > 20 J)

ICD: Implantable cardioverter defibrillator; HV: High-voltage.

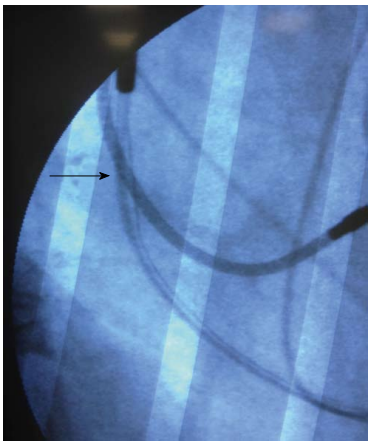

Figure 1 Cable externalization in patient 1.

without inducing VF). The decision to perform R-wave-synchronized shock instead of classical DFT was based on patient risk profile (high risk of complications from VF induction). The remaining 16 patients were non tested, at the time of manuscript draft, due to different clinical reasons: Patient's refusal (n° 1), low risk patients or low risk leads (n° 6), severe comorbidities/very old age (n° 9). The shock test was performed under sedation with Midazolam in all cases. In patients with atrial fibrillation or flutter the test was performed only if optimal anticoagulation could be confirmed. All patients gave their consent and the study was approved by the Institutional Board of our Department.

RESULTS

Twelve patients (80% of those undergoing the test, 7 with EC) had a normal behavior during the shock: In 8 cases of DFT (5 with EC), with VF induction, the arrhythmia was correctly detected and treated; in 4 cases of R-wave-synchronized shock (2 with EC) electrical parameters (in particular HV impedance) remained normal and stable. At 6 mo follow-up none of these patients died or experienced electrical failure of the lead.

Three patients (20%) failed the test. One patient with EC had a sudden drop of HV impedance (< 10 Ohm) after a 25J R-wave-synchronized shock, so a new defibrillation lead was implanted without complications. Two other patients with EC, undergoing DFT, showed a short-circuit during shock delivery and the ICD was unable to interrupt VF (they were externally defibrillated).

Among the 16 patients who were *not* tested 4 died of non-cardiac causes (cancer), 4 died of end-stage heart failure, 8 continued to have their lead functional (at 6 mo follow-up). The two cases with failed DFT are described in details hereinafter.

Case 1

A 75-year-old man with ischemic dilated cardiomyopathy had received a St Jude Medical biventricular defibrillator in 2009 for primary prevention (Promote™ RF 3213). Defibrillation lead was a 7Fr Riata™ ST 7000, dual-coil, active fixation. At the time of implant, a defibrillation testing had been successfully performed. During routine scheduled device interrogations electrical parameters had always been stable and normal. In accordance with AIAC recommendations we performed a complete fluoroscopic evaluation in three views each 6 mo. In 2013 we discovered an initial, mild conductors' externalization, type 1-2 according to Parvathanemi's fluoroscopic grading score[8], near the proximal coil. In 2014 the externalization worsened, becoming a type 3 (> 1 cm length extrusion, Figure 1) with extension toward ventricular coil; nevertheless, electrical parameters remained normal and stable. At this point we decided to check system integrity performing a defibrillation testing: Under sedation VF was induced with a shock-on-T; the arrhythmia was correctly sensed and detected but two consecutive internal shocks (20 and 36 J) were unsuccessful (Figures 2 and 3); an external 200J biphasic shock promptly restored sinus rhythm (arrow, Figure 3). Post-shock ICD interrogation revealed very low HV impedance during shock delivery (< 10 Ohms) and warning messages on programmer screen: "Problem with HV electrodes", "High current drainage during HV therapy". Further analysis showed truncated ineffective shocks, likely due to device protection circuitry after recording HV impedance < 10 Ohms. The patient underwent uneventful lead extraction; notably, at visual inspection, there was no sign of abrasion or externalization between the lead and the ICD can. Unfortunately, neither the extracted lead (seriously damaged during the procedure) nor the generator were sent to the manufacturer for further analysis.

Case 2

A 64-year-old man with ischemic dilated cardiomyopathy had received a St Jude Medical single-chamber defibrillator in 2008 for primary prevention (Epic™

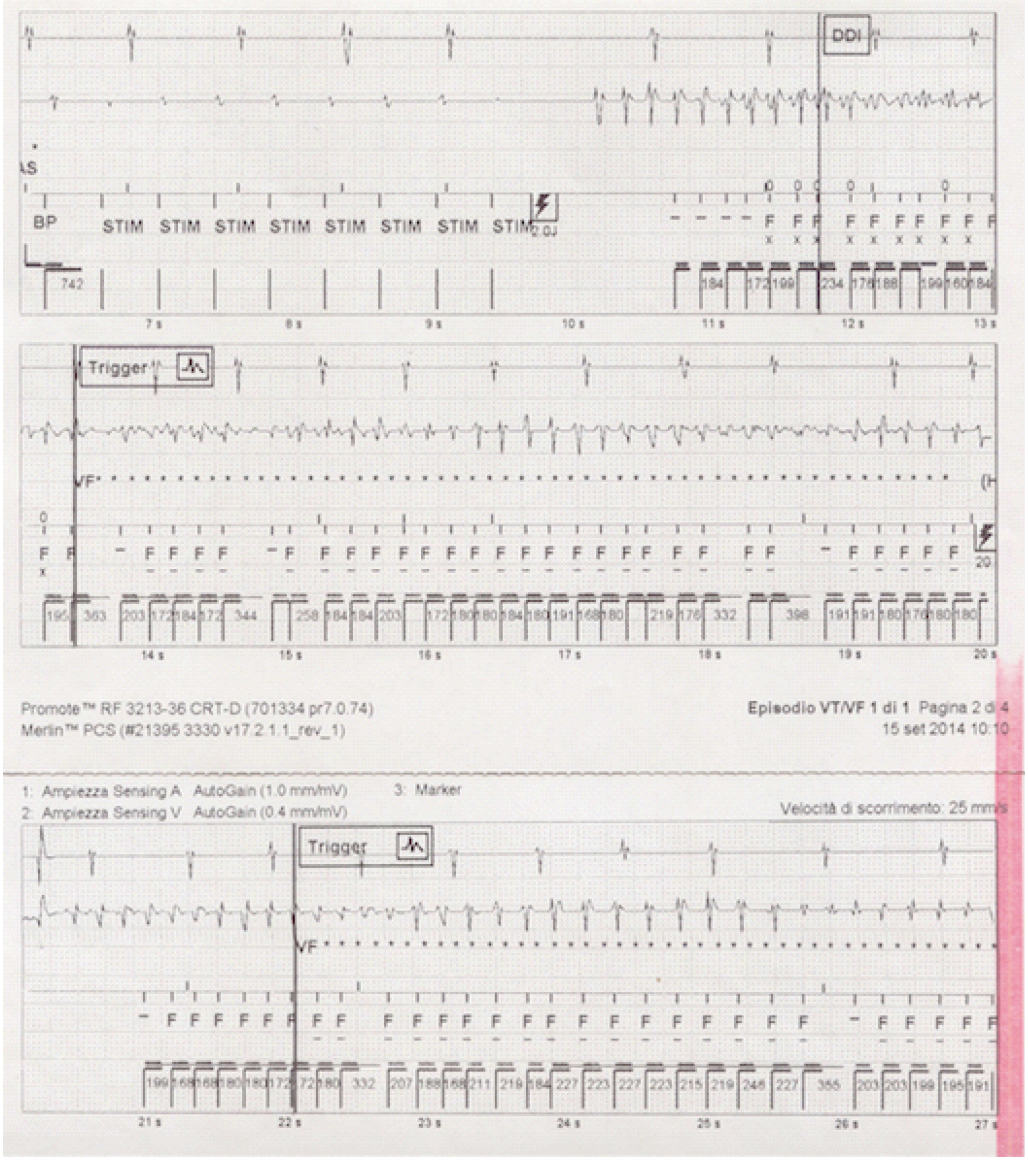

Figure 2 Patient 1: Induction of ventricular fibrillation with shock-on-T and failed defibrillation at 20 J.

VR197). Defibrillation lead was an 8Fr Riata™ 1571, dual-coil, passive fixation. At the time of implant, a defibrillation testing had been successfully performed. During routine device interrogations, electrical parameters of the lead had always been stable and normal. Notably in Epic™ family HV impedance cannot be measured automatically with a painless sub-threshold test, but requires a true shock at 12 Volts (< 0.1 J) synchronized with the QRS complex. In 2014 the patient was hospitalized for elective pulse generator change. At this time fluoroscopy showed conductors externalization, type 2 according to Parvathaneni *et al*[8]'s grading score, near the ventricular coil (Figure 4). For this reason, we decided to perform a defibrillation testing before the generator replacement, even if we could expect a prolonged charging time (battery charge time about 20"). Under sedation VF was induced with DC Fibber™, that delivers a single, direct current pulse through HV electrodes. A very "bad" VF was induced (Figure 5) with very low and fragmentated QRS complexes; however the arrhythmia was correctly sensed and detected. After a long charge time (> 28") a 30J shock was delivered but it did not interrupt VF. So an external 200J biphasic shock was promptly delivered, with resumption of sinus rhythm only after the third attempt. Post-shock ICD interrogation revealed no detectable HV impedance during shock delivery and warning messages on programmer screen: "HV impedance not detectable", "High current drainage during HV therapy", "Charge time limit reached", "Delivered shock truncated at 12 ms". As impedance was not detectable during the defibrillation testing, we decided to check it with a "routine" HV lead impedance (HVLI) test, the same test performed during routine ambulatory interrogation. Figure 6 shows what happened: Soon after the delivery of 12 V (arrow, Figure 6) VF restarted and again we promptly delivered external 200 J biphasic shock, and again sinus rhythm was restored

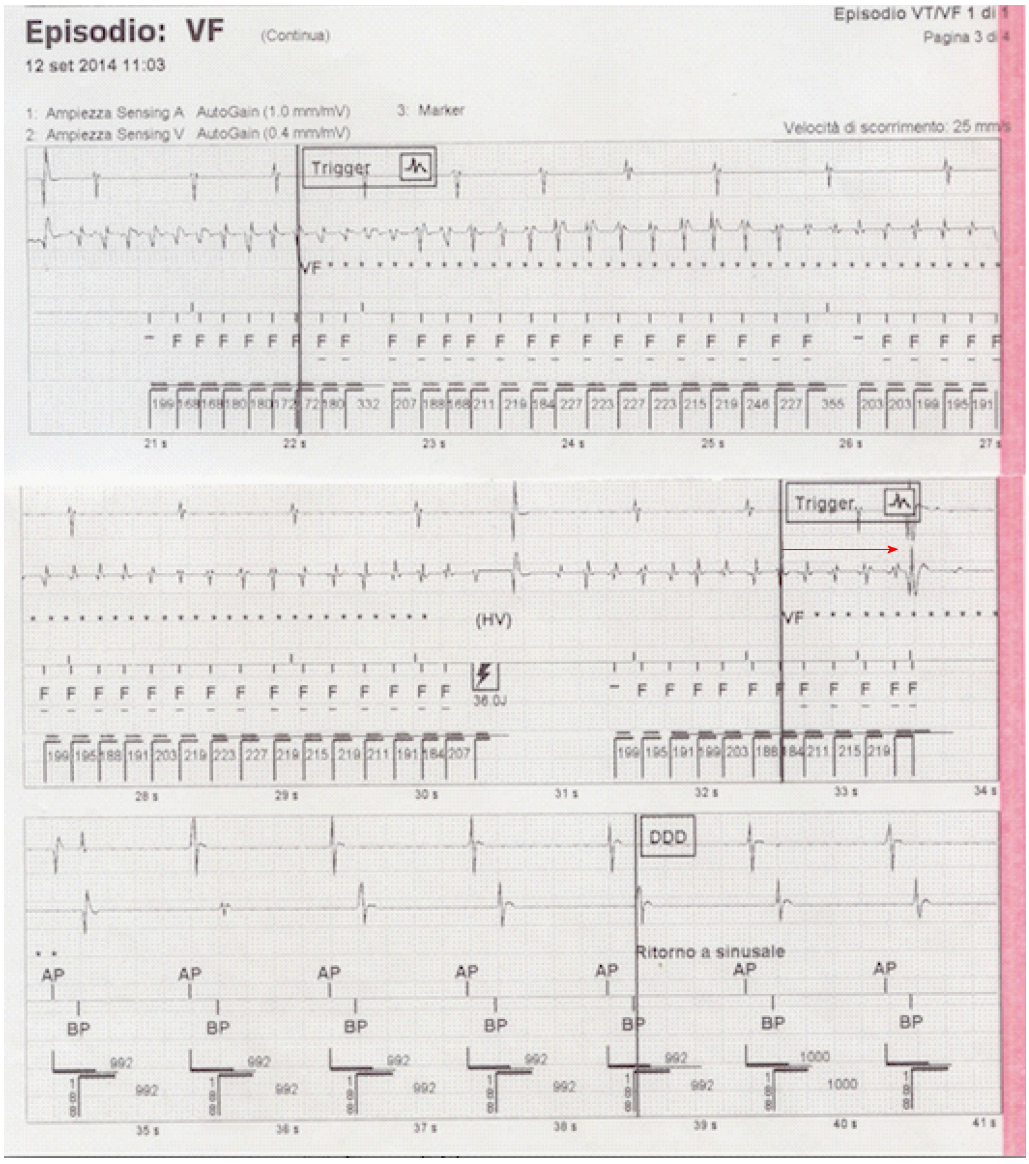

Figure 3 Patient 1: Failed defibrillation at 36 J; external 200 J biphasic shock promptly restored sinus rhythm (arrow).

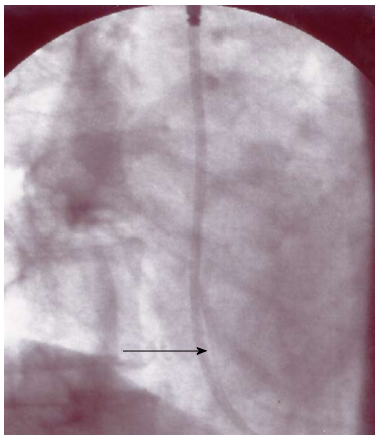

Figure 4 Cable externalization in patient 2.

only after the third attempt. During manual external defibrillation the ICD tried to deliver its own shock at 30 J that was ineffective: Post-shock interrogation showed a truncated shock with HV impedance < 10 Ohms. Luckily the patient recovered well after this "arrhythmic storm" and he subsequently underwent an uneventful lead extraction. At visual inspection there was no sign of abrasion or externalization between the lead and the ICD can. Unfortunately, also in this case, neither the extracted lead nor the generator were sent to the manufacturer.

DISCUSSION

Structural and electrical failure in Riata™ leads

Riata™ and Riata ST™ leads have a multilumen construction that includes paired HV and pace-sense cables (anode-ring) covered with 1.5 mL of ethylenetetrafluoroethylene (ETFE) and strung through individual lumens that run the length of the silicone body; the central pace-sense coil (cathode-tip), with stylet lumen encased, is further wrapped in a tube of polytetrafluoroethylene. The body of lead is insulated

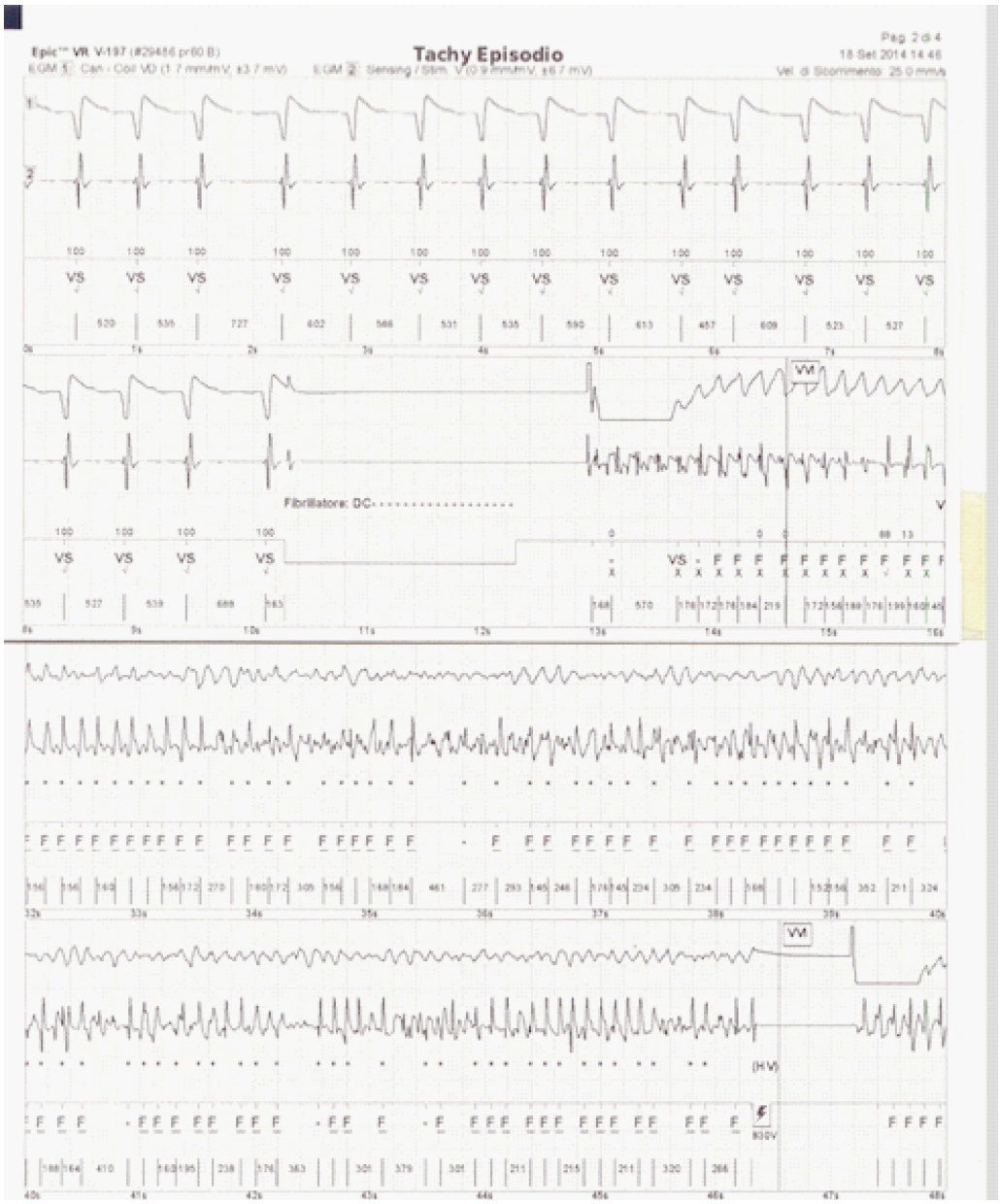

Figure 5 Patient 2: Induction of ventricular fibrillation with DC Fibber™ and failed defibrillation at 30 J.

with pure silicone rubber that has an increased risk of abrasion[1,6]. The anatomy of these leads accounts for the mechanism of externalization caused by the movement of the redundant cables within their lumen ("inside-out" abrasion). 8Fr single-coil leads are more prone to externalization: This can be explained by the design with two lumens directly opposed to one another, whereas dual-coil and ST models have three lumens equally spaced around the central coil, which reduces tension[9]. Importantly, in about 25% of cases (especially dual-coil), externalization is not evident on fluoroscopy because "inside-out" abrasion occurs underneath the shocking coils.

The risk for the patients is mainly linked to electrical failure[1,6] ranging from 1.3%[2] to 17.3%[10]. In our experience electrical abnormalities were found in 15% of patients, the majority with 8Fr leads. Increased pacing threshold appears earlier, while impedance changes occur later; overall noise and sensing issues are the most common electrical dysfunctions[1,5]. Short circuits and failure to defibrillate are rare but potentially lethal complications: It is disturbing that such shorts can occur without any other previous electrical abnormality, sometimes being the first and only sign of failure, also in absence of externalization[1,5-7].

In our two patients the cause of the short circuits cannot be explained with certainty, as the leads were not sent to manufacturer for further analysis. It is possible that the short took place in correspondence to the externalized cables, but "inside-out" abrasion underneath a shocking coil could not be excluded. An insulation break under a shocking coil can cause friction and abrasion of ETFE, with bare cables coming in contact with the HV conductors: The shock can

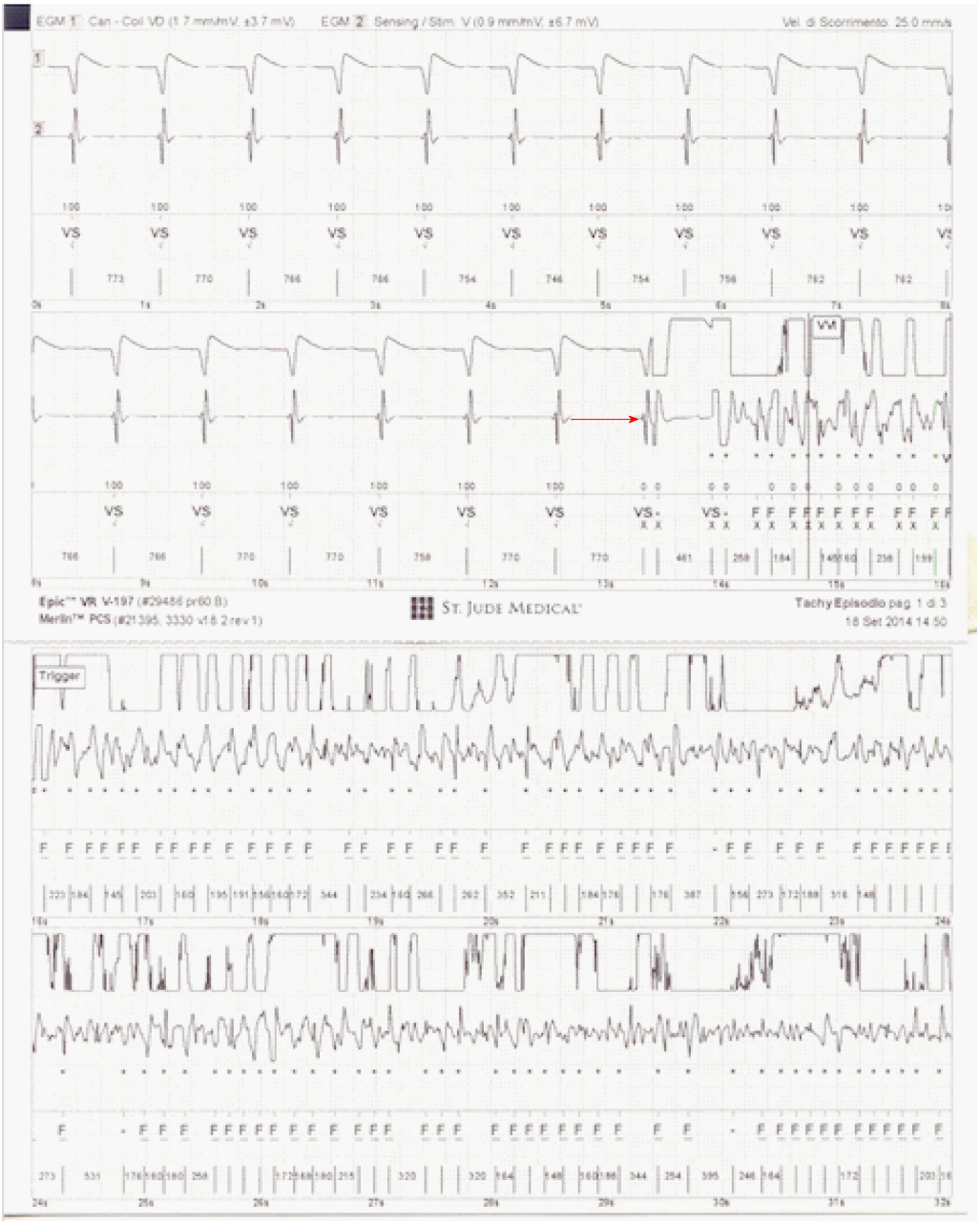

Figure 6 Patient 2: Ventricular fibrillation unintentionally re-induced after high-voltage impedance test with a synchronized 12 V shock (arrow).

be shorted, melting the cable and the coil, and fails to defibrillate[7]. In more than 65% of cases multiple insulation defects are present on each single lead[1]. Moreover, in 15%-22% of electrical failures the abrasion occurs between the lead and the can in the pocket or as a consequence of "outside-in" abrasion (contact with another lead or anatomic structures)[1,5]. In our patients "lead-to-can" abrasion could be reasonably excluded as there was no sign of abrasion/externalization between the lead and the can at a careful visual inspection.

"Lead-to-can", "outside-in" abrasion and ETFE disruption underneath shocking coils are the mechanisms that explain electrical failures and shorts in leads without visible externalization.

In the Multicenter Riata Evaluation Study[2], in Hauser's experience[5] and in another work[10] the prevalence of electrical dysfunction was not associated with EC. In our Center 37% of electrical failures occurred without EC, all in 8Fr dual-coil leads.

Some other studies have shown that leads with EC were more prone to electrical dysfunction, in particular lower R waves[4,6,11]. A recent prospective observational study showed[12] that the incidence of new electrical dysfunction was 6.4% at 12 mo and was associated with EC. Also in Danish experience EC was associated with a higher risk of electrical abnormalities[13]. Finally, Zeitler *et al*[6] in a recent meta-analysis of 23 observational studies, showed that the presence of EC was associated with a more than 6-fold increase in the rate of electrical failure compared to no EC.

Role of defibrillation or HV shock testing

When EC is evident, or when other mechanisms expose the cables, the lead may still function normally because HV and pace-sense ring cables are covered with ETFE, which serves as a second insulation. However, if ETFE abrades, electrical short circuits can occur during shock delivery with potential catastrophic consequences[1,5]. The delivery of a low current during routine measurement of HV impedance may not reveal a small short circuit, that can only be evident by attempting to deliver a true shock for spontaneous arrhythmias or in the context of a HV defibrillation testing[1,2]. Moreover HVLI test, during routine ambulatory evaluation, is not without risk: In our patient n° 2 VF was unintentionally re-induced during HV impedance test with a synchronized 12 Volts shock. This disturbing phenomenon had already been described by Hauser *et al*[5]: A patient, with an 8Fr dual-coil 1581 model, died from VF induced by HVLI test and not terminated by the ICD.

Given this very complex background the clinical decision regarding patients with Riata™ leads is troubling, particularly when managing "apparently" functional leads. Routine follow up (including home monitoring, programming additional far-field and noise reversion electrograms, tightening HV lead impedance limits) may be insufficient to detect such failure[5].

The potential role of defibrillation testing in the management of Riata™ is currently unclear and has been poorly studied; only sparse reports are available in literature[14-19]. Some authors advocate it at time of pulse generator change[1,4,6,7] but patients at high risk could benefit from the test even before that time.

Leong *et al*[14] was the first to describe a case of failure to deliver an appropriate shock by a 8Fr dual-coil 1570 Riata™ (implanted 8 years before) during a DFT performed after generator replacement; lead measurements were normal and stable, in absence of EC. The lead was not extracted but product analysis report of the generator indicated structural damage by a short circuit in the lead, while lead connection with the header box appeared normal.

Subsequently, Doshi *et al*[15] described an 8Fr dual-coil 1580 Riata™, with known externalization but no prior electrical abnormality, which was unable to deliver HV shock to interrupt VF at DFT after ICD replacement. After the failed shock HV impedance dropped to < 10 Ohms. The lead was extracted and its analysis revealed that the short in the HV circuit occurred underneath the caval coil.

In the report by Webber *et al*[16] another failure to defibrillate induced VF was described, again at the time of battery depletion. The lead was an 8Fr dual-coil 1580 Riata™, implanted 8 years before, without signs of malfunction (no externalization) but with decreasing R wave amplitude over time. Induced VF was correctly sensed and detected, the device charged 36 J but delivered 0.6 J first and 0 J at second attempt; post-shock impedance was < 20 Ohms. The lead was not extracted and the generator not analyzed by the manufacturer, but the normal appearance of the insulation in the lead segment looped beneath the generator suggested a short circuit within the intravascular/intracardiac body of the lead.

Shah *et al*[17] presented a case of failure to deliver effective shock during DFT by an 8Fr dual-coil 1581 lead, implanted 8 years before, with moderate EC and prior normal electrical parameters. This failure was discovered incidentally while the device was attempting to deliver an inappropriate shock for a supraventricular tachycardia; shock delivery was truncated and HV impedance dropped to < 10 Ohms. The subsequent DFT failed to interrupt VF. The patient refused extraction and a new lead was implanted; careful visual inspection of the proximal part of the lead did not reveal any insulation defect in the pocket.

Lakshmanadoss *et al*[18] described two cases of failed DFT at time of generator replacement: Both leads were 1581 models, a dual-coil and a single-coil (implanted 5 years before). The two leads displayed normal baseline electrical parameters in absence of externalization. In both cases delivery of shock was aborted due to loss of HV impedance and short circuit. The leads were explanted and the first was analyzed by the manufacturer: Superior vena cava coil and HV cable-to-ventricular coil were melted, confirming a short circuit due to an internal insulation defect not apparent on fluoroscopy.

Shen *et al*[19] described their experience with externalized leads and normal baseline electrical measures. Fifteen-out-23 patients with EC received a recent HV shock: 2 patients for spontaneous ventricular arrhythmias, 5 during scheduled defibrillation testing, 8 during an elective synchronized HV shock. Only one patient (6%) demonstrated post-shock electrical failure. An important finding from this study is that system integrity was checked with a commanded HV synchronized shock, without inducing VF, in 8-out-15 patients.

It is intriguing that, in these reports, the leads were all (except one) dual-coil models 1570-1580-1581. Moreover, in four cases there was no sign of externalization on fluoroscopy[14,16,18]. Our two patients had a 1571-8Fr and a 7000ST-7Fr, both dual-coil, both with EC. Are dual-coil leads more prone to short circuits and electrical failure in general? Numbers are small so we have no definitive answers, but the hypothesis is plausible given the failure mechanisms described above. Also in Hauser's experience[1,5] the vast majority of shorts occurred in dual-coil models, independently of EC. In the meta-analysis by Zeitler *et al*[6] rates of both EC and electrical failure were higher in dual-coil *vs* single-coil leads. However, Valk *et al*[20] found that electrical failure of single-coil was 17%, compared to 7% for dual-coil models, but they did not address short circuit in particular.

Externalized conductors are only the "tip of the iceberg" of the "Riata history". The association between

EC and electrical failure is still controversial but it is clear that these leads have a proclivity to failure. When an overt electrical dysfunction is present the lead has to be replaced or removed, independently of EC. When the lead seems to function normally (routine ambulatory check) management should be individualized and the factors to consider are: Presence/absence of externalization; lead's characteristics (model, implant duration, degree of externalization and its worsening over time); patient's high risk profile (secondary prevention, pacemaker dependency, recent/prior ICD intervention, young age, long life expectancy). Due to the failure mechanisms and the possibility of a short circuit, defibrillation testing should be considered as an important tool to check Riata™ integrity. Based on our experience and literature review, we believe that all patients with an electrically intact Riata™ lead should undergo such test at least at the time of generator replacement. If induction of VF is contraindicated, or too risky for the patient, an alternative "stress test" for the lead could be a commanded synchronized HV shock (preferably > 20 J) with a lower risk of inducing VF[21,22]. Some patients at high risk should be advised to undergo a HV shock testing even before the time of generator change. For example, if a patient has received a recent/prior effective shock for spontaneous arrhythmias a DFT should be considered within 6-12 mo: The reason is that when the ETFE is only partially abraded, a first shock may defibrillate but subsequent shocks may fail if the remaining ETFE breaks thereafter. HV shock testing should be advised also for "high risk leads": Presence of externalization (especially if worsening over time); minimal changes in electrical parameters (impedance changes < 25%, intermittent non-sustained noise from non-physiological signals); some models (8Fr, dual coil, 1570-1580-1590 families). Many questions remain unanswered: Are dual-coil leads more prone to shorts and electrical dysfunction? When and how often to perform a HV shock test? Is long-term outcome of patients undergoing the test better than non-tested patients? Future studies are needed to define the best strategy for the management of Riata™ leads with normal baseline electrical parameters, with and without EC[23]. Table 1 summarizes potential indications for HV shock testing in this setting.

The main limitations of our study are the small sample size, the retrospective nature, the empirical selection of patients for HV shock test. Moreover, neither the extracted leads nor the generators were sent to the manufacturer for further analysis.

COMMENTS

Background

The management of the recalled Riata™ defibrillator leads is complex and optimal treatment is often carried out on individual basis.

Research frontiers

The potential role of high-voltage shock testing for management of Riata™ defibrillator leads has been poorly studied, only sparse reports being available in literature. The research hotspot is to evaluate how shock testing can impact on patient outcome.

Innovations and breakthroughs

In Riata™ leads the delivery of a low current during routine measurement of high-voltage impedance may not reveal a small short circuit, that can only be evident by attempting to deliver a true shock, either for spontaneous arrhythmias or in the context of a shock testing.

Applications

Defibrillation testing (or alternatively synchronized shock) should be considered an important tool to check Riata™ integrity.

Terminology

Riata™ defibrillator leads are prone to a unique failure mechanism: The conductors can externalize through the silicone insulation ("inside-out" abrasion) and appear outside the lead body leading to electrical failure. Routine electrical measures may miss small short circuits. Defibrillation testing consists in inducing ventricular fibrillation (VF) and waiting for the implantable cardioverter defibrillator to defibrillate it. R-wave-synchronized shock is a less invasive testing that delivers a high-voltage shock to check the system, but does not induce VF.

Peer-review

This interesting article is a comprehensive discussion about management of Riata defibrillator lead. It is a very important study, about an important issue for which there is much heterogeneity in management.

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ORIGINAL ARTICLE

Observational Study

Increased levels of circulating platelet-derived microparticles in psoriasis: Possible implications for the associated cardiovascular risk

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Abstract

AIM

To evaluate platelet activation markers in psoriasis patients, compared to controls, and investigate their association with the inflammatory burden of psoriasis.

METHODS

Forty psoriatic patients without cardiovascular disease,

and 12 healthy controls were subjected to measurement of baseline platelet CD62P, CD63 and CD42b expression, platelet-leukocyte complexes, *i.e.*, platelet-monocyte complexes (PMC), platelet-neutrophil complexes (PNC) and platelet-lymphocyte complexes, and concentrations of platelet-derived microparticles (PMPs) using flow cytometry. Both larger-size (0.5-0.9 μm) and smaller-size (< 0.5 μm) PMPs were determined. Serum interleukin (IL)-12 and IL-17 levels were also measured by enzyme-linked immunosorbent assay. The severity of psoriasis was evaluated by the Psoriasis Area Severity Index (PASI).

RESULTS

PMP concentrations were significantly higher in psoriasis patients than controls [mean ± standard error of mean (SEM): 22 ± 5/μL *vs* 11 ± 6/μL; $P = 0.018$), for both smaller-size (10 ± 2/μL *vs* 4 ± 2/μL; $P = 0.033$) and larger-size (12 ± 3/μL *vs* 6 ± 4/μL; $P = 0.014$) PMPs. Platelet CD62P, CD63 and CD42b expression and circulating PMC and PNC were similar between the two groups. Lower circulating PLC were observed in psoriasis patients compared to controls (mean ± SEM: 16% ± 3% *vs* 23% ± 6%; $P = 0.047$). Larger-size PMPs were related with IL-12 levels ($P < 0.001$) and smaller-size PMPs with both IL-12 and IL-17 levels ($P < 0.001$). Total PMPs also correlated with IL-12 ($P < 0.001$). CD63 expression was positively correlated with both IL-12 and IL-17 ($P < 0.05$). Increased PASI score was associated with increased levels of larger-size PMPs ($r = 0.45$; $P = 0.011$) and increased CD63 expression ($r = 0.47$; $P < 0.01$).

CONCLUSION

PMPs, known to be predictive of cardiovascular outcomes, are increased in psoriasis patients, and associated with high inflammatory disease burden. Enhanced platelet activation may be the missing link leading to cardiovascular events in psoriatic patients.

Key words: Psoriasis; Atherosclerosis; Inflammation; Platelet activation; Platelet-derived microparticles

Core tip: Psoriasis is associated with increased risk of cardiovascular disease. The pathogenic mechanisms shared by the two diseases seem to converge onto "inflammation" phenomenon. Platelets have a potent role in inflammation. Herein we evaluated platelet activation in psoriasis patients compared to healthy controls, and investigated a potential association between platelet activation markers and the inflammatory burden of psoriasis, the latter assessed by serum levels of pivotal pro-inflammatory cytokines implicated in psoriasis. We conclude that the association between psoriasis and atherosclerosis may be related to excessive platelet-derived microparticles (PMPs) formation. The size class of PMPs was taken into consideration in our study.

Papadavid E, Diamanti K, Spathis A, Varoudi M, Andreadou I, Gravanis K, Theodoropoulos K, Karakitsos P, Lekakis J, Rigopoulos D, Ikonomidis I. Increased levels of circulating platelet-derived microparticles in psoriasis: Possible implications for the associated cardiovascular risk. *World J Cardiol* 2016; 8(11): 667-675 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i11/667.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i11.667

INTRODUCTION

Psoriasis is now considered as an immune-mediated inflammatory disease of the skin affecting about 3% of the adult general population[1]. Although primarily a cutaneous disease, recent research implicates its association with systemic inflammation resulting in increased risk for atherosclerosis and subsequent cardiovascular disease (CVD)[2,3]. The detailed pathophysiological mechanisms which lead psoriasis patients to atherosclerosis remain unclear; however the common inflammatory milieu the two diseases share is of rising significance[3,4].

Hemostasis-maintaining platelets also have relevant functions in inflammation, with recent evidence showing that thrombosis and inflammation are in fact two intrinsically linked processes[5]. Pathomechanisms of psoriasis involve platelet activation, as reported by several investigators so far[6-9]. Increased platelet activation is also implicated in atherosclerotic plaque formation and plaque destabilization[10,11]. Activation of platelets is associated with their degranulation and the subsequent surface expression of antigens, such as CD62P (P-selectin) and CD63, the decreased surface expression of CD42b (GPIb alpha)[12], and the formation of platelet-leukocyte complexes[13]. In addition, the so-called platelet-derived microparticles (PMPs)[14] constitute a marker of platelet activation which, in recent years, has gained emerging importance. PMPs are membrane vesicles of a diameter of 0.1 to 1 μm generated from activated platelets in an exocytotic budding process. They display procoagulant and atherosclerotic properties, being reported to possess 50- to 100-fold higher specific procoagulant activity than activated platelets themselves[15]. PMPs are involved in inflammatory diseases[16], as well as in atherosclerosis and CVD[17,18]. Besides platelet activation, the chronic inflammatory burden of psoriatic patients may also be the trigger for the development of CVD, with interleukin (IL)-12 and IL-17 implicated in the pathogenesis of both diseases[19-21]. Interestingly, IL-17 has recently been shown to facilitate platelet aggregation[22].

Five studies so far have shown elevated PMPs in psoriasis patients[7,8,23-25], two of them methodologically limited in PMP detection by using ELISA-based assays[7,24]. PMPs were also shown, albeit not always[8,23,25], to correlate with the activity of psoriasis, as assessed by the Psoriasis Area Severity Index (PASI) score[7,24]. However,

a possible association of platelet activation with cytokines identified as key players in psoriasis has not yet been examined, to the best of our knowledge. Therefore, the purpose of this investigation was to evaluate platelet activation markers in patients with psoriasis without overt cardiovascular complications, compared to healthy controls, by means of flow cytometry, and to determine the relationship between marker levels and the pro-inflammatory cytokine profile of psoriasis, as this was assessed by IL-12 and IL-17 levels.

MATERIALS AND METHODS

Study population

This hospital-based cross-sectional study was carried out in 40 patients with psoriasis without coronary artery disease (CAD), and 12 participants selected as healthy controls with age, sex, atherosclerotic risk factors (hypertension, hyperlipidemia, current smoking) and use of anti-hypertensive or lipid-lowering medication, similar to those of the patients with psoriasis (Table 1). Eligible patients were given a diagnosis of plaque psoriasis for at least 6 mo. None of them had received relevant topical medications during the two weeks prior to the study and prior systemic therapy, if any, was interrupted for adequate wash-out period. Exclusion criteria for patients with psoriasis and healthy donors included disorders or drugs affecting platelet activity or likely to influence the outcome of the study, namely obstructive CAD (as defined by the absence of clinical history, angina, and reversible myocardial ischemia during a treadmill test and stress echocardiography), chronic inflammatory disease, psoriatic arthritis, familial hyperlipidemia, diabetes mellitus, moderate or severe valvular heart disease, primary cardiomyopathies, chronic renal failure, malignancies and the use of anti-platelet drugs and systemic steroids. All patients underwent exercise treadmill test and/or stress echocardiography as well as carotid and peripheral artery ultrasonography before blood sampling to exclude the presence of clinical significant CVD. Psoriasis patients were recruited from the inpatients' section and the outpatients' clinics of the Department of Dermatology and Venereology of our hospital, while controls were selected from visitors and hospital staff. Written informed consent was obtained from all participants before enrollment in the study. This study was conducted according to the Declaration of Helsinki principles, and was approved by the medical ethical committee of Athens University.

Blood collection

To avoid artificial platelet activation during collection of samples, blood was taken from the antecubital vein through a 21G needle following light application of a tourniquet; the first 2 mL of blood were discarded to avoid procedurally-induced platelet activation. Subsequently, 4 mL of blood were collected in plastic tubes without anticoagulant for assay of serum IL-12 and IL-17. Finally, 4.5 mL of whole blood were drawn into Vacutainer tubes containing 3.2% sodium citrate stock solution (1:9 volume) and mixed immediately, avoiding frothing during the procedure, for the estimation of platelet activation markers by means of flow cytometry within 45 min after blood collection. All patients and controls had ceased antihypertensive treatment and statins 48 h before blood sampling.

Table 1 Clinical characteristics of the study population

Variable	Psoriasis (n = 40)	Controls (n = 12)	P value
Age, yr	51 ± 12	49 ± 13	0.8
Sex (male) (%)	25 (63)	7 (58)	0.8
PASI score	11 ± 7	-	-
Risk factors (%)			
Hypertension	14 (35)	4 (33)	0.9
Hyperlipidemia	14 (35)	4 (33)	0.9
Current smoking	19 (48)	5 (42)	0.8
Medications (%)			
Anti-hypertensives	13 (33)	4 (33)	0.9
Statins	16 (40)	5 (42)	0.9

Flow cytometry

We examined platelet activation state using several markers because it is recognized that platelet activation is a complex process and measuring the classical degranulation markers alone may limit the ability to detect platelet activation under all circumstances.

Platelet surface markers: Platelet membrane glycoproteins (GPs) expression was measured from whole blood. Five microliter of blood diluted to 100 μL with PBS per tube were incubated with CD36-PE and FITC labeled monoclonal antibodies against platelet markers that may be expressed in the basal state (CD41, CD42b, CD61) and markers that may be expressed upon activation (CD62P, CD63) (Biolegend, United States) for 10 min at room temperature. One milliliter of PBS was added and samples were analyzed *via* flow cytometry. Gating was performed using a forward/side scatter (FSC/SSC) dot plot. Expression levels were measured for low FSC/SSC with CD36 positivity using the percentage of platelets with fluorescence over the cutoff set by running 4 samples from control patients (Figure 1A).

PMPs: The technique used for PMP quantification was adapted from a previously described method[26,27]. Plasma was separated from whole blood by centrifugation at 1500 *g* for 15 min. Recovered plasma was centrifuged for 2 min at 13000 *g*. Microparticles were labeled using FITC-conjugated Annexin V and PE-conjugated CD41 (Biolegend, United States). Fluorescent-conjugated isotype antibodies were used as controls and a suitable set of beads (Megamix, Biocytex, France) containing three types of beads with a defined size (0.5, 0.9 and 3 μm diameter) was used to identify microparticles *via* FSC/SSC and determine two PMP-size regions (0.5-0.9 μm and < 0.5 μm PMPs). Samples were diluted to 1 mL using binding buffer and analyzed

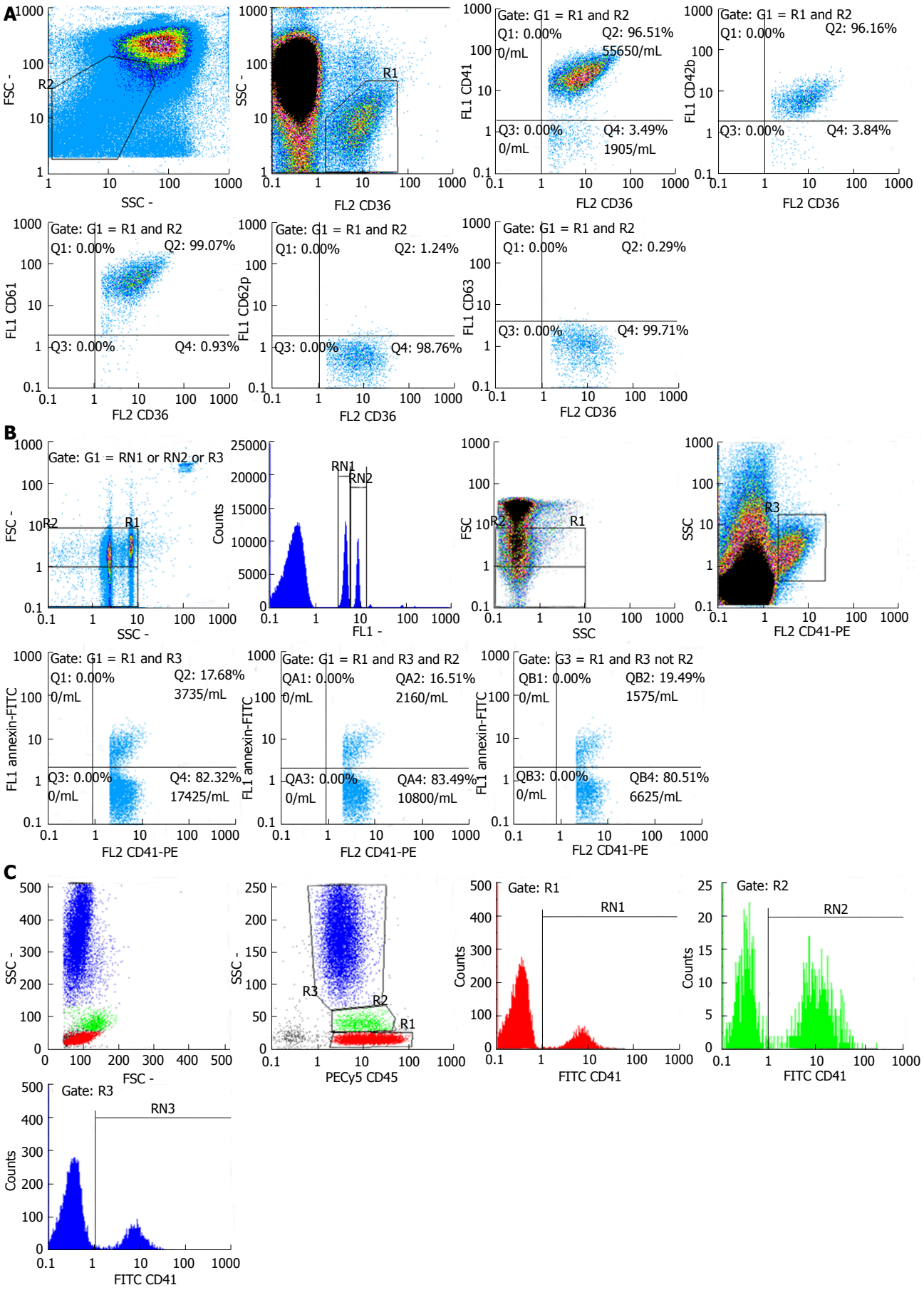

Figure 1 Flow cytometric analysis of platelet membrane glycoproteins, platelet-derived microparticles and platelet-leukocyte aggregates. A: Flow cytometric analysis of membrane-bound glycoproteins. Analysis of each GP was performed on particles of FSC/SSC of platelets (R2) expressing CD36 (R1); B: Beads for gating of microparticles of 0.5 μm (left population), 0.9 μm (right population) and 3 μm (upper right population). Same gating strategy was used to identify PMPs of 0-0.5 μm (R1 and R3 not R2), 0.5-0.9 μm (R1 and R2 and R3) or PMPs in general (R1 and R3); C: Platelet-leukocyte aggregates calculated for lymphocytes (red), monocytes (green) and granulocytes (blue).

using absolute counting, when available, on a Partec Cyflow (Partec, Munster, Germany) *via* volumetric count. PMPs were identified as dual-positive Annexin V-FITC/CD41-PE events in the microparticle region and count/μL was calculated *via* multiplying the count/mL of the cytometer with the dilution factor of 50 divided by 1000 (Figure 1B).

Platelet-leukocyte complexes: In order to analyze platelet-monocyte complexes (PMC), platelet-neutrophil complexes (PNC) and platelet-lymphocyte complexes (PLC), 100 μL of whole blood, 20 μL of FITC-conjugated anti-CD41 (or negative control antibody) and 20 μL of PECy5-conjugated anti-CD45 (Biolegend, United States) were added into each tube, gently mixed, and incubated in dark, at room temperature for 15 min. Erythrocyte lysis was performed using 2 mL of Quicklysis solution (Cytogons, Spain). Samples were analyzed on a Partec Cyflow Space (Partec, Munster, Germany) within 30 min. Leukocyte populations were gated on a SSC/CD45-PECy5 dot plot and aggregates for each population were calculated as the percentage of monocytes, neutrophils and lymphocytes which were CD41-positive (Figure 1C).

Soluble IL-12 and IL-17

IL-12 was measured in serum using a commercially available kit (Human IL-12 p70 Quantikine HS ELISA Kit; R and D Systems, Minneapolis, United States). This assay detects values as low as 0.5 pg/mL. IL-17 serum levels were also measured by high-sensitivity immunoassay (Human IL-17A High Sensitivity ELISA; eBioscience, Vienna, Austria). The lower limit of detection of the assay was 0.01 pg/mL.

Statistical analysis

The independent-samples *t* test was performed to determine the significance level for differences between patient and control groups. Data were expressed as mean ± standard error of mean (SEM). Correlation testing (using Spearman rank correlation coefficient) was performed to assess the strength of relationships between multiple variables. A probability value of < 0.05 was taken to be statistically significant. Statistical Package for Social Sciences version 22.0 (IBM, Chicago, IL) was used for the analysis.

RESULTS

Baseline characteristics of the study population

We did not observe any significant difference in baseline characteristics between the two groups (Table 1).

Markers of platelet activation

Activation-dependent surface change: No significant difference was observed in CD62P, CD63 or CD42b expression between the two study groups. Mean ± SEM for the fraction of platelets expressing CD62P and CD63 in psoriasis patients and controls were 7 ± 2 *vs* 6 ± 3; $P = 0.748$ and 5 ± 2 *vs* 3 ± 2; $P = 0.791$, respectively. Mean ± SEM for the fractions of platelets with reduced expression of CD42b was 8 ± 2 *vs* 10 ± 7; $P = 0.397$ for psoriasis patients and controls, respectively (Table 2).

PMPs: PMP concentrations were markedly higher in psoriasis patients compared to controls (mean ± SEM: 22 ± 5/μL *vs* 11 ± 6/μL; $P = 0.018$). When considering PMP size, both smaller-size (mean ± SEM: 10 ± 2/μL *vs* 4 ± 2/μL; $P = 0.033$) and larger-size (12 ± 3/μL *vs* 6 ± 4/μL; $P = 0.014$) PMPs were higher in patients compared to healthy subjects (Table 2).

Platelet-leukocyte complexes: There was no significant difference in the percentage of circulating neutrophils or monocytes in whole blood which formed complexes with platelets between the two groups (mean ± SEM for PMC and PNC in psoriasis patients and controls respectively were 38% ± 4% and 27% ± 3% *vs* 33% ± 6% and 29% ± 5%; $P = 0.723$ and $P = 0.775$, respectively). However, significantly lower circulating PLC were observed in psoriasis patients (mean ± SEM: 16% ± 3% *vs* 23% ± 6%; $P = 0.047$) (Table 2).

Relationship between platelet activation marker levels and the inflammatory burden of psoriasis

A significant correlation was established between larger-size PMPs and IL-12 levels ($r = 0.55$; $P < 0.001$) and between smaller-size PMPs and levels of both IL-12 and IL-17 ($r = 0.58$ and $r = 0.49$ respectively; $P < 0.001$). Total PMPs also correlated with IL-12 levels ($r = 0.56$; $P < 0.001$). CD63 expression correlated well with levels of both IL-12 and IL-17 ($r = 0.46$; $P = 0.011$ and $r = 0.43$; $P = 0.015$, respectively). Increased PASI score was associated with increased levels of larger-size PMPs ($r = 0.45$; $P = 0.011$) and increased CD63 expression ($r = 0.47$; $P < 0.01$). Circulating PLC were found to be negatively correlated with PMPs ($r = -0.44$; $P = 0.002$), both with smaller-size ($r = -0.28$; $P = 0.048$) and larger-size ($r = -0.4$; $P = 0.005$) PMPs.

DISCUSSION

The exact mechanism of predisposition to CVD in psoriasis *per se* has not been fully elucidated so far. However, several lines of evidence highlight the potent role inflammation plays. Indeed, psoriasis patients, in addition to chronic skin inflammation, display a higher prevalence of CVD risk factors and metabolic syndrome components[28] which lead to systemic inflammation, and therefore atherosclerosis, CVD and myocardial infarction[2,3]. Platelets have an important role in increasing inflammation, and pathogenetic mechanisms of both psoriasis and atherosclerosis may involve platelet activation[6-11,23-25]. The present study demonstrated that circulating platelets are in a state of activation in patients with psoriasis without clinically evident CVD compared to healthy subjects, as shown by a significant increase in circulating PMPs. It reinforces previous findings of

Table 2 Markers of platelet activation and inflammatory markers in the study population

Marker	Psoriasis (n = 40)	Controls (n = 12)	P value
CD42b negative platelets (%)	8 ± 2	10 ± 7	0.397
CD62P positive platelets (%)	7 ± 2	6 ± 3	0.748
CD63 positive platelets (%)	5 ± 2	3 ± 2	0.791
Total AV+/CD41+ PMPs[1]	22 ± 5	11 ± 6	0.018[3]
< 0.5 μm AV+/CD41+ PMPs[1]	10 ± 2	4 ± 2	0.033[3]
0.5-0.9 μm AV+/CD41+ PMPs[1]	12 ± 3	6 ± 4	0.014[3]
Platelet-lymphocyte complexes (%)	16 ± 3	23 ± 6	0.047[3]
Platelet-monocyte complexes (%)	38 ± 4	33 ± 6	0.723
Platelet-neutrophil complexes (%)	27 ± 3	29 ± 5	0.775
IL-12[2]	19 ± 0.5	2 ± 0.3	< 0.001[3]
IL-17[2]	3 ± 0.4	0 ± 0.1	< 0.001[3]

Results are expressed as the mean number ± standard error of mean. [1]Results are expressed in microparticles per plasma microlitre; [2]Results are expressed in pg/mL; [3]Values are statistically significant. AV: Annexin V; PMPs: Platelet-derived microparticles; IL: Interleukin.

elevated circulating PMP levels in psoriasis patients[7,8,23-25] and adds to those findings by demonstrating for the first time, to the best of our knowledge, a positive relationship between PMP concentrations and high inflammatory psoriasis burden, as this was assessed by IL-12 and IL-17 levels, suggesting a close association between PMPs and psoriasis activity. It is also the first study to report a higher level of larger-size PMPs, in addition to small-size ones, in psoriasis patients. It is now accepted that PMPs are separated into four size classes with different active components and different functional effects on platelets and endothelial cells[29], and therefore, elucidation of the size class(es) involved in psoriasis can help clarify PMP involvement in the disease and the mechanisms implicated in exertion of their effects. Pelletier *et al*[8] had previously showed that only small-size PMPs are increased in psoriasis. The discrepancy with our results may be related to the different working definition of blood-derived PMPs in the two studies, based on the prerequisite or not of Annexin V (a phospholipid-binding protein that binds to exposed phosphatidylserine on the surface of activated platelets) binding. Annexin V positive PMPs are documented to elicit pro-coagulant activity, in contrast to little or no such activity possessed by Annexin V negative PMPs[30].

PMPs are involved in CAD by binding to the endothelium, submatrix of the vascular wall and leukocytes, thereby facilitating thrombus propagation[17,18,31]. They are also known to cause endothelial dysfunction[32]. In the setting of psoriasis *per se*, PMPs may well contribute to leukocyte recruitment in psoriatic skin lesions, given their known ability to increase leukocyte adhesion to the endothelium and to promote leukocyte activation by modulating leukocyte-leukocyte and leukocyte-endothelial cell interactions[5]. Taken together, elevated levels of PMPs observed in psoriasis patients may be the contributory factor to development of atherosclerosis and the increased cardiovascular risk in those patients by triggering a cascade of events.

In the present study, PMPs proved to be the most "sensitive" index of platelet activation, whereas the classical platelet activation markers CD62P, CD63 and CD42b were not altered. To our knowledge, CD63 or CD42b expression in psoriasis had not been investigated so far. In contrast to our CD62P results, three previous studies have shown enhanced CD62P surface expression in psoriasis[6,9,33]. One other study was in concordance with our findings[34]. Although P-selectin has been considered by many the "gold standard" marker of platelet activation, it was shown that degranulated, P-selectin-positive platelets rapidly lose surface P-selectin to the plasma pool *in vivo*[35,36]. Therefore, platelets may circulate in an increased state of activation but express normal levels of CD62P. In fact, it has been proposed that CD62P is a more reliable tool for monitoring platelet function at acute but not chronic stimulus of platelets[37]. The majority of our patients did not have a flare of their disease at the time of our study. Regarding platelet-leukocyte complexes as a marker of platelet activation, there is only one previous study measuring PMC and PNC in psoriasis[34], also not managing to highlight a significant increase. There is no report in the literature concerning PLC in psoriasis, to the best of our knowledge. In the setting of CVD, it has been suggested that the formation of PMC is related to the development of atherosclerotic complications being a sensitive marker of platelet activation[38]. Contrary to our expectations for increased PLC in psoriasis pointing to platelet activation, lower PLC were measured in the bloodstream of our psoriasis patients compared to healthy controls. Our finding could be attributed to the adhesion of PLC in the inflamed skin microvasculature, on asymptomatic atherosclerotic lesions or both. Therefore, decreased blood concentration could merely reflect increased sequestration of the generated platelet-lymphocyte aggregates on the vessel wall. With regard to this, it has already been shown *in vivo* that increased leukocyte rolling in murine skin and subsequent extravasation is due to the aggregate formation of platelets with mononuclear leukocytes[6]. Interestingly, a negative correlation was established in our study between PMP levels and circulating PLC.

Chronic inflammatory skin diseases and atherosclerosis share common pathogenic features in which pro-inflammatory cytokines play an important role[3,4,39]. In the inflammatory microenvironment present in psoriasis, IL-12 and IL-17 are of crucial importance[19]. This is underlined by the fact that the biologic agents ustekinumab and secukinumab are targeted against IL-12 and IL-17, respectively. IL-12 leads to the differentiation of type 1 T helper (Th1) lymphocytes, whereas IL-17A and IL-17F, secreted by type 17 T helper (Th17) cells, activate keratinocytes and induce the production of antimicrobial peptides. Notably, recent interest has focused particularly on IL-17-producing Th17 cells[40]. This cell type is specialized in immunosurveillance of epithelium, and it also secretes

IL-22, a key cytokine linking adaptive immune effectors and epithelial dysregulation in psoriasis. Amelioration of epidermal hyperplasia during successful anti-TNF treatment is associated with reduced Th17 responses. Based on the current knowledge, it appears that Th17 cells are responsible for many of the inflammatory and autoimmune responses once attributed to Th1 lymphocytes. Apart from their implication in psoriasis pathogenesis, IL-12 and IL-17 are also involved in the development of atherosclerosis[20,21,41]. In this viewpoint, IL-12 and IL-17 release into the circulation by cell populations in inflamed psoriatic skin could exert harmful atherosclerotic effects. Taken the aforementioned data into consideration, the association of platelet activation markers, namely PMPs and CD63, with the levels of pro-inflammatory cytokines IL-12 and IL-17, demonstrated in our study, comes as no surprise. Interestingly, it has been recently shown that IL-17A can promote platelet function in patients with acute coronary syndrome *via* activating platelets ERK2 signaling pathway and may provide a novel target for antiplatelet therapies in CAD[22]. On the basis of the ability of IL-17A to promote platelet function, the view that inflammation and platelet activation perpetuate each other and cascade to the development of atherosclerosis is reinforced.

Features of psoriasis pathogenesis, including chronic inflammation and the proven platelet activation, may contribute to atherosclerotic risk in psoriasis. Our study has shown increased levels of PMPs, a marker of platelet activation, in psoriasis patients without overt CVD compared to healthy controls. This difference has been demonstrated for the first time in both smaller-size and larger-size PMPs. As PMPs express procoagulant phospatidylserine activities, facilitate thrombus propagation and provoke endothelial cell damage, elevated PMP levels could provide one of the missing links leading to increased cardiovascular risk in psoriasis. Furthermore, PMPs were higher in those patients with high inflammatory disease burden, as this was assessed by IL-12 and IL-17 levels, as well as in those patients with high PASI score, suggesting a close association between PMPs and psoriasis activity. Given the ability of IL-17A to promote platelet function, this finding is in favor of the view that inflammation and platelet activation may perpetuate each other and cascade to the development of atherosclerosis. Finally, we identified the presence of lower PLC in the bloodstream of psoriasis patients which could be attributed to their adhesion in the inflamed skin microvasculature, on asymptomatic atherosclerotic lesions or both. PLC levels negatively correlated with PMP levels. The clinical relevance of our findings, however, remains still disputed. While there is ample *in vitro* evidence of the potential downstream biological effects of microparticles (*e.g.*, promotion of coagulation, regulation of inflammation, vascular damage)[42], many of which are known to be important in atherogenesis, *in vivo* data in patients with psoriasis are lacking. In this setting, PMP generation could merely represent an epiphenomenon related to the inflammation of psoriasis with little *in vivo* biological activity. Future studies are needed to address whether PMPs are simply biomarkers of inflammatory disease or have a role in psoriasis pathophysiology leading to accelerated atherosclerosis.

The small number of controls and the absence of age/sex matching between patients and controls should be acknowledged as study limitations.

In conclusion, PMPs, known to be predictive of cardiovascular outcomes, are increased in psoriasis patients, and associated with high inflammatory disease burden. Enhanced platelet activation may be the missing link leading to cardiovascular events in psoriatic patients.

COMMENTS

Background

Psoriasis is a common immune-mediated inflammatory disease of the skin. Although primarily a cutaneous disease, recent research implicates its association with systemic inflammation resulting in increased risk for atherosclerosis and subsequent cardiovascular disease (CVD). Platelets have an important role in inflammation. Pathogenic mechanisms of both psoriasis and atherosclerosis seem to involve platelet activation.

Research frontiers

Enhanced platelet activation in psoriasis patients has already been established, but a potential association between platelet activation markers and the inflammatory burden of psoriasis has not yet been examined.

Innovations and breakthroughs

The present study demonstrated increased platelet activation in patients with psoriasis without clinically evident CVD compared to healthy controls, as shown by a significant increase in circulating platelet-derived microparticles (PMPs), a platelet activation marker which is known to be predictive of cardiovascular outcomes. It reinforces previous findings of elevated circulating PMP levels in psoriasis patients and adds to those findings by demonstrating for the first time, to the best of our knowledge, a positive relationship between PMP concentrations and levels of cytokines identified as key players in psoriasis, namely interleukin (IL)-12 and IL-17, suggesting a close association between PMPs and high inflammatory disease burden. Given the ability of IL-17A to promote platelet function, this finding is in favor of the view that inflammation and platelet activation may perpetuate each other culminating in the development of atherosclerosis. Furthermore, this is the first study, to the best of our knowledge, to report a higher level of larger-size PMPs, additionally to small-size ones, in psoriasis patients. It is now accepted that PMPs are separated into four size classes with different active components and different functional effects on platelets and endothelial cells, and therefore, elucidation of the size class(es) involved in psoriasis can help clarify PMP involvement in the disease and the mechanisms implicated in exertion of their effects. Taken together, the study concludes that the association between psoriasis and atherosclerosis may be related to excessive PMP formation.

Applications

Enhanced platelet activation may be the missing link leading to cardiovascular events in psoriatic patients. Future studies are needed to address the *in vivo* biological activity of PMPs contributing to CVD in patients with psoriasis, as well as the potential role of anti-platelet medications in psoriasis in the context of reducing both psoriasis activity and atherosclerotic risk.

Terminology

PMPs constitute a marker of platelet activation which, in tecent years, has gained emerging importance. PMPs are membrane vesicles of a diameter of 0.1 to 1 μm generated from activated platelets in an exocytotic budding process.

They display procoagulant and atherosclerotic properties, being reported to possess 50- to 100-fold higher specific procoagulant activity than activated platelets themselves.

Peer-review

Interesting and very relevant study regarding the level of markers of platelet activation in psoriasis.

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ORIGINAL ARTICLE

Prospective Study

Outcomes and long-term survival of coronary artery surgery: The controversial role of opium as risk marker

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Abstract

AIM

To study survival in isolated coronary artery bypass graft (CABG) patients and to evaluate the impact of preoperative chronic opium consumption on long-term outcome.

METHODS

Cohort of 566 isolated CABG patients as Tehran Heart Center cardiac output measurement was conducted. Daily evaluation until discharge as well as 4- and 12-mo and 6.5-year follow-up information for survival status were fulfilled for all patients. Long-term 6.5-year overall and opium-stratified survival, adjusted survival curves based on opium consumption as well as possible predictors of all-cause mortality using multiple cox regression were determined by statistical analysis.

RESULTS

Six point five-year overall survival was 91.8%; 86.6% in opium consumers and 92.7% in non-opium consumers (P = 0.035). Patients with positive history of opium consumption significantly tended to have lower ejection fraction (EF), higher creatinine level and higher prevalence of myocardial infarction. Multiple predictors of all-cause mortality included age, body mass index, EF, diabetes mellitus and cerebrovascular accident. The hazard ratio (HR) of 2.09 for the risk of mortality in opium addicted patients with a borderline P value (P = 0.052) was calculated in this model. Further adjustment with stratification based on smoking and opium addiction reduced the HR to 1.20 (P = 0.355).

CONCLUSION

Simultaneous impact of smoking as a confounding variable in most of the patients prevents from definitive judgment on the role of opium as an independent contributing factor in worse long-term survival of CABG patients in addition to advanced age, low EF, diabetes mellitus and cerebrovascular accident. Meanwhile, our findings do not confirm any cardio protective role for opium to improve outcome in coronary patients with the history of smoking. Further studies are needed to clarify pure effect of opium and warrant the aforementioned findings.

Key words: Coronary artery bypass; Outcomes; Survival analysis; Opium; Hazards models

Core tip: A significant percentage of coronary artery disease patients undergo cardiac surgery so defining outcome predictors is essential for risk calculation and is necessary for estimation of resource utilization and provision of services. Employing global knowledge on this issue is not justified without adjustment for regional specifications and needs. This study aimed at clarifying the role of opium addiction in predicting long-term mortality of coronary artery bypass graft surgery in addition to advanced age, low ejection fraction, diabetes mellitus and cerebrovascular accident.

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INTRODUCTION

Growing number of patients undergoing coronary artery bypass graft (CABG) surgery all over the world[1], justifies studying on possible predicting factors of clinical outcomes such as short and long-term survival. There are published reports of some predictive factors responsible for short-term mortality such as advanced age, previous history of cardiac surgery and myocardial infarction, non-cardiac comorbidities, New York Heart Association functional class (FC) III or IV and serum creatinine (Cr) level[2,3]. Also some additional factors have been suggested for intermediate-term mortality including left ventricular ejection fraction (EF) and history of percutaneous coronary stenting[2,4]. Similarly, long-term survival could be influenced by diabetes mellitus[5], hypoalbuminemia[6], female gender, smoking, cardiogenic shock[7] and severe preoperative renal dysfunction[3,8].

Coronary artery disease (CAD) has a high prevalence in Iranian population, affecting 22.2% of men and 37.5% of women[9]. In addition, opium is the major abused substance in Iran[10] and the prevalence of opium addiction is believed to be higher in CAD patients undergoing revascularization[11]. The predictive role of opium in short-term outcomes of patients undergoing CABG is controversial. Some investigations have suggested cardiac protective role for opium during ischemic events[12,13]. In a propensity-matched study, Sadeghian *et al*[14] found no association between opium dependence and post CABG in-hospital complications. On the other hand, in Safaii *et al*[15]'s study, six months post-CABG readmission was significantly more frequent in opium users. However, there are few evidences to clarify the definite relationship between chronic opium abuse and long-term survival in cardiac surgery patients.

So not only there is limited knowledge regarding the adverse impact of opium consumption on long-term survival of CABG patients, but also the available studies on short-term outcomes have shown controversial results. Therefore in this study we aimed to assess the impact of chronic opium consumption on long-term survival of patients who underwent isolated CABG in a cardiac tertiary center.

MATERIALS AND METHODS

Patients and methods

In the present cohort study (Tehran Heart Center Cardiac Output Measurement)[16], 566 consecutive CAD patients who underwent isolated CABG during six months (April 2006-September 2006) at THC, a high-volume specialized heart tertiary care center, were identified and after signing the informed consent were entered the study. Exclusion criteria were concomitant replacement or repair of heart valve, ventricular aneurism resection or any surgeries other than CABG.

Data collection

Patients' demographic characteristics including age, gender, weight, waist circumference, body mass index (BMI) as well as their initial laboratory measurements were recorded in previously defined data sheets and were completed from THC surgery database[17] in case of

missing information. Family and drug history, associated comorbidities, habitual habits, FC and left ventricular EF were also among documented variables. Regular daily consumption of opium along with fulfilling DSM-IV-TR criteria for opium dependence was considered for opium addiction[11,18].

EuroSCORE was also calculated for all study population and were categorized as low risk (0-2), medium risk (3-5), high risk (6-8) and very high risk (≥ 9) based on what has been previously reported in literature[19,20].

Follow-up

CABG Patients were followed at 4 and 12 mo following the operation through the organized regular visits at CABG follow-up clinic or by telephone interviews. Meanwhile, any outpatient or inpatient services thereafter are recorded precisely in patients' electronic medical file at our institution by the initial unique code. But for the specific purpose of our study in evaluation of long-term survival, we contacted patients by telephone to attend at hospital to be followed 7 years after the cardiac surgery. The precise date of patients' attendance was recorded.

In these long-term follow-up sessions, all patients were investigated for survival status. FC and EF along with further laboratory assessments were also assessed. For non-responders, mortality tracking as well as the exact time and to somehow the etiology of death was noted through telephone interviews with patients' relatives or by checking up the online registration of deaths. For surviving non-responders, the last attendance at THC for receiving any services was considered as the last time of follow-up. The latter group was defined as incomplete follow-up.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD) or median with 25^{th} and 75^{th} percentiles, and were compared between two groups of opium usage using independent samples *t* or Mann-Whitney *U* test. Categorical variables were expressed as frequency and percentage and were compared between aforementioned groups applying χ^2 or Fisher's exact test. Survival probabilities were estimated using Kaplan-Meier method and their 95%CI were calculated through log-transformed method. The univariate effect of variables on long-term mortality was evaluated using Cox proportional hazards (PH) regression. All variables with *P* values less than 0.2 in the univariate analysis were candidate to enter the multivariable model. A backward stepwise Cox PH model, with removal and entry probabilities as 0.1 and 0.05 respectively, was applied to find the multiple predictors of long-term mortality. The PH assumption was checked through the χ^2 test of the correlation coefficient between transformed survival time and scaled Schoenfeld residuals. Those variables which simultaneously associated with opium usage and long-term mortality with *P* values less than 0.2 were detected as potential confounders. The effect of opium on long-term mortality adjusted for potential confounders was assessed using Cox PH model. All effects on long-term mortality were reported through hazards ratio (HR) with 95%CI. Softwares IBM SPSS statistics for windows version 22 (Armonk, NY: IBM Corp.) and STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.) were used to conduct the analyses.

RESULTS

Based on findings, among 566 patients, 53 (9.4%) deaths occurred during the 6.5 years of follow-up among which 40.9% was cardiac and 59.1% was of non-cardiac cause. Median follow-up time for all of the study population was 78.7 mo (95%CI: 78.5-78.9). Median (25^{th}-75^{th} interquartile range) follow-up time of 235 patients with incomplete follow-up was 74.6 (25^{th}-75^{th}: 73.5-75.7) mo.

Patients' demographics characteristics and risk factors: Table 1 demonstrates patients' baseline demographic and clinical characteristics by survival status. According to univariate analysis, age, blood urea nitrogen and high-density lipoprotein levels were significantly lower and EF, albumin and triglyceride levels were significantly higher among survivors. Moreover, opium consumption, diabetes mellitus, cerebrovascular accident and peripheral vascular disease were significantly more frequent among the expired cases.

The frequency of moderate, high and very high risk EuroSCORE was significantly higher in non-survivors as compared to survivors. However, the number of diseased vessels and performed bypass grafts was similar between the both groups.

Table 2 shows patients' baseline demographic and clinical characteristics generally and based on opium consumption. Mean ± SD age of patients was 59.08 ± 8.9 years and 75.1% were men. History of opium consumption was present in 14.5%. Forty-one percent had diabetes mellitus and 3.9% had history of cerebrovascular accident. Body mass index and EF mean ± SD was 27.3 ± 4.08 kg/m^2 and 48.5% ± 10.3%, respectively. Functional class Ⅲ was documented in 14.7% of patients. Opium users were significantly more often men, younger, smoker and also alcohol consumer.

Patients with positive history of opium consumption also significantly tended to have lower EF (44.9 ± 9.4 *vs* 49.1 ± 10.3), higher Cr (1.3 ± 0.3 *vs* 1.2 ± 0.2) and higher prevalence of MI (71.6% *vs* 47.5%). On the other hand, the level of BMI and fasting blood sugar and prevalence of hyperlipidemia (HLP), hypertension were significantly lower in these patients.

Opium-stratified survival

Based on follow-up information, 6.5 years (78.7 mo) overall survival was 91.8% (95%CI: 89.5%-94.2%). When analyzed based on habitual history of opium consumption, 6.5-year (78.7 mo) overall survival was

Table 1 Basic demographic and clinical characteristics of patients, univariate analysis for overall survival using Cox regression

	Alive (n = 513)	Dead (n = 53)	Hazard ratio (95%CI)	P value
Age (yr)	58.5 ± 8.81	64.6 ± 8.27	1.08 (1.044-1.117)	< 0.001
Gender (male)	382 (74.5)	43 (81.1)	1.425 (0.716-2.837)	0.313
BMI (kg/m^2)	27.4 ± 4.04	26.5 ± 4.39	0.947 (0.881-1.019)	0.146
Waist circumference (cm)	101.3 ± 1.46	100.2 ± 2.95	0.962 (0.85-1.09)	0.543
FC				0.141
I	177 (34.6)	21 (39.6)		
II	263 (51.5)	20 (37.7)	0.701 (0.379-1.295)	0.256
III	71 (13.9)	12 (22.6)	1.433 (0.702-2.924)	0.323
EF (%)	49.1 ± 10.07	42.2 ± 11.07	0.94 (0.915-0.965)	< 0.001
FH	251 (49.1)	18 (34)	0.5 (0.282-0.887)	0.018
Smoking	183 (35.8)	20 (37.7)	0.954 (0.542-1.678)	0.870
Alcohol	66 (13.7)	5 (9.8)	0.523 (0.201-1.363)	0.185
Opium	69 (13.5)	13 (24.5)	1.939 (1.032-3.644)	0.040
DM	204 (39.9)	28 (52.8)	1.789 (1.033-3.097)	0.038
HLP	366 (71.6)	32 (60.4)	0.58 (0.334-1.008)	0.053
HTN	253 (49.5)	26 (49.1)	1.033 (0.602-1.774)	0.906
CVA	16 (3.1)	6 (11.3)	4.146 (1.761-9.76)	0.001
PVD	136 (26.6)	22 (41.5)	2.166 (1.246-3.766)	0.006
MI	254 (49.9)	32 (61.5)	1.61 (0.92-2.816)	0.095
Alb (g/dL)	4.6 ± 0.32	4.5 ± 0.39	0.351 (0.16-0.77)	0.009
FBS	96 (87-117)	98 (84-124)	1.004 (0.997-1.011)	0.266
BUN	38 (31-46)	40 (33-52)	1.035 (1.016-1.054)	< 0.001
Cr	1.2 ± 0.27	1.3 ± 0.26	2.009 (0.832-4.856)	0.121
Mg	1.9 ± 0.34	1.9 ± 0.39	1.15 (0.421-3.143)	0.785
HCT	42.3 ± 5.92	42.8 ± 3.82	1.013 (0.979-1.047)	0.462
TG	165 (115-210)	126 (97-173)	0.994 (0.990-0.999)	0.010
Chol	160 ± 44.86	166.3 ± 48.06	1.003 (0.997-1.008)	0.347
LP	23 (12-45)	28 (15-54)	1.006 (0.997-1.016)	0.191
CRP	5.75 (4.9-7)	6.35 (4.82-8.57)	1.001 (0.99-1.013)	0.814
LDL	82 (59-105)	86 (68-114)	1.003 (0.997-1.009)	0.280
HDL	40.3 ± 8.5	42.8 ± 9.37	1.031 (1-1.062)	0.049
No. of diseased vessel				0.473
1	19 (3.7)	2 (3.8)		
2	99 (19.4)	7 (13.2)	0.616 (0.127-2.976)	0.547
3	393 (76.9)	44 (83)	1.013 (0.245-4.191)	0.985
No. of grafts	3.7 ± 0.94	3.9 ± 1.02	1.234 (0.922-1.650)	0.158
Euro score				0.017
Low (0-2)	301 (58.9)	20 (37.7)		
Moderate (3-5)	171 (33.5)	25 (47.2)	2.089 (1.160-3.762)	0.014
High (6-8)	32 (6.3)	6 (11.3)	2.851 (1.143-7.110)	0.025
Very high (≥ 9)	7 (1.4)	2 (3.8)	4.479 (1.044-19.220)	0.044

Data are shown as mean ± SD, median (25th-75th percentiles) or number (%). BMI: Body mass index; FC: Functional class; EF: Ejection fraction; FH: Family history; DM: Diabetes mellitus; HLP: Hyperlipidemia; HTN: Hypertension; CVA: Cerebrovascular accident; PVD: Peripheral vascular disease; MI: Myocardial infarction; Alb: Albumin; FBS: Fasting blood sugar; BUN: Blood urea nitrogen; Cr: Creatinine; Mg: Magnesium; HCT: Hematocrit; TG: Triglyceride; Chol: Cholestrol; LP: Lipoprotein; CRP: C-reactive protein; LDL: Low density lipoprotein; HDL: High density lipoprotein.

found to be 86.6% (95%CI: 79.1%-94.7%) in opium users and 92.7% (95%CI: 90.3%-95.1%) in non-opium users.

After adjustments for confounding variables such as age, BMI, EF, diabetes, alcohol, HLP, MI, Cr, BUN and EuroSCORE, we found an evidence of predicting mortality for opium with a borderline P value (HR = 2.16; 95%CI: 0.96-4.84; P = 0.06) (Figure 1). As appears from curves, opium users have a trend to worse long-term survival as compared to non-opium consumers.

Multiple predictors of all-cause mortality

Multiple Cox regression for predictors of all-cause mortality is described in Table 3. As demonstrated, age, BMI, EF, diabetes mellitus and cerebrovascular accident remained the significant independent predictors of all-cause mortality. We found a trend of increasing risk of all-cause mortality by increasing age and functional class. A converse trend for all-cause mortality was noted by increasing BMI and EF. As shown, cerebrovascular accident had the greatest HR for mortality (HR = 3.45; 95%CI: 1.3-9.1, P = 0.013).

Smoking rate was not significantly different between survivors and non-survivors (Table 1). However, due to high coincidence of smoking and opium addiction (Table 2) we adjusted the results by adding the history of smoking to the list of predictors of long-term mortality which reduced the HR of opium for mortality from 2.09

Table 2 Baseline characteristics of patients base on opium consumption

	All patients (*n* = 566)	Opium + (*n* = 82)	Opium - (*n* = 484)	*P* value
Age (yr)	59.08 ± 8.9	55.9 ± 8.3	59.6 ± 8.9	< 0.001
Gender (male)	425 (75.1)	80 (97.6)	345 (71.3)	< 0.001
BMI (kg/m^2)	27.3 ± 4.08	25.7 ± 3.6	27.6 ± 4.08	< 0.001
Waist circumference (cm)	101.3 ± 11.3	100.3 ± 9.3	101.5 ± 11.6	0.514
FC				0.531
I	198 (35)	33 (40.2)	165 (34.2)	
II	283 (50)	39 (47.6)	244 (50.6)	
III	83 (14.7)	10 (12.2)	73 (15.1)	
EF (%)	48.5 ± 10.3	44.9 ± 9.4	49.1 ± 10.3	0.001
FH	269 (47.5)	44 (53.7)	225 (46.7)	0.242
Smoking	203 (35.9)	67 (81.7)	136 (28.2)	< 0.001
Alcohol	71 (12.5)	29 (37.7)	42 (9.2)	< 0.001
DM	232 (41)	26 (31.7)	206 (42.7)	0.061
HLP	398 (70.3)	48 (58.5)	350 (72.6)	0.010
HTN	279 (49.3)	30 (36.6)	249 (51.7)	0.012
CVA	22 (3.9)	4 (4.9)	18 (3.7)	0.545
PVD	158 (27.9)	21 (25.6)	137 (28.4)	0.600
MI	286 (50.5)	58 (71.6)	228 (47.5)	< 0.001
Alb (g/dL)	4.6 ± 0.3	4.5 ± 0.3	4.6 ± 0.3	0.200
FBS	96 (87-118)	92 (81-106)	97 (88-119)	0.011
BUN	38 (31-46)	35 (27-42)	39 (32-47)	0.004
Cr	1.2 ± 0.2	1.3 ± 0.3	1.2 ± 0.2	0.024
Mg	1.9 ± 0.3	1.8 ± 0.3	1.9 ± 0.3	0.314
HCT	42.3 ± 5.7	42.2 ± 3.6	42.4 ± 6.04	0.848
TG	159 (113-205)	150 (107-194)	162 (113-208)	0.353
Chol	157 (129-186)	156 (124-177)	157 (129-188)	0.167
LP	23 (12-46)	24 (9-44)	23 (13-47)	0.432
CRP	5.8 (4.9-7.2)	5.8 (4.8-7.1)	5.8 (4.9-7.2)	0.617
LDL	83 (60-106)	85 (60.7-100.5)	82.5 (60-110)	0.517
HDL	40.5 ± 8.6	39.4 ± 8.5	40.7 ± 8.6	0.205
No. of diseased vessel				0.733
1	21 (307)	2 (2.4)	19 (3.9)	
2	106 (18.7)	17 (20.7)	89 (18.5)	
3	437 (77.2)	63 (76.8)	374 (77.6)	
No. of grafts	4 (3-4)	4 (3-5)	4 (3-4)	0.400
Euro score				0.199
Low (0-2)	321 (56.7)	45 (54.9)	276 (57.3)	
Moderate (3-5)	196 (34.6)	26 (31.7)	170 (35.5)	
High (6-8)	38 (6.7)	10 (12.2)	28 (5.8)	
Very high (≥ 9)	9 (1.6)	1 (1.2)	8 (1.7)	

Data are shown as mean ± SD, median (25th-75th percentiles) or number (%). BMI: Body mass index; FC: Functional class; EF: Ejection fraction; FH: Family history; DM: Diabetes mellitus; HLP: Hyperlipidemia; HTN: Hypertension; CVA: Cerebrovascular accident; PVD: Peripheral vascular disease; MI: Myocardial infarction; Alb: Albumin; FBS: Fasting blood sugar; BUN: Blood urea nitrogen; Cr: Creatinine; Mg: Magnesium; HCT: Hematocrit; TG: Triglyceride; Chol: Cholesterol; LP: Lipoprotein; CRP: C-reactive protein; LDL: Low density lipoprotein; HDL: High density lipoprotein.

to 1.20 (95%CI: 0.819-1.745, *P* = 0.355) (Table 3).

Table 3 Multivariable model for all-cause mortality using Cox regression

	Hazard ratio (95%CI)	*P* value
Age (per 10 yr increase)	2.46 (1.64-3.70)	< 0.001
Opium	2.09 (0.99-4.39)	0.052
BMI	0.89 (0.82-0.96)	0.004
FC		0.653
II *vs* I	0.86 (0.44-1.66)	0.653
III *vs* II	2.18 (0.97-4.88)	0.057
EF (per 5% increase)	0.71 (0.62-0.81)	< 0.001
DM	2.97 (1.59-5.54)	0.001
CVA	3.45 (1.30-9.16)	0.013

BMI: Body mass index; FC: Functional class; EF: Ejection fraction; DM: Diabetes mellitus; CVA: Cerebrovascular accident.

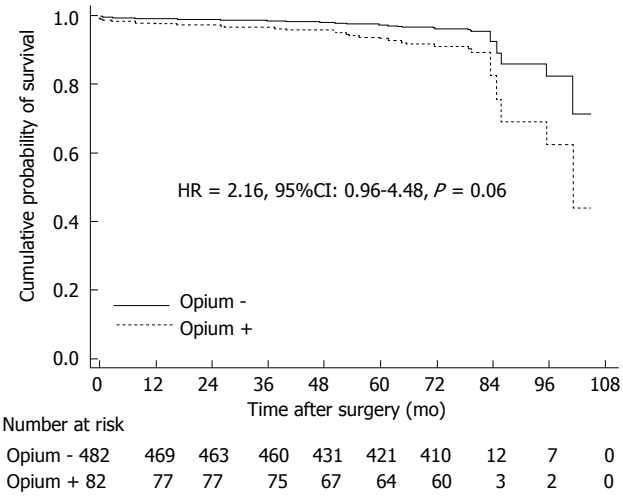

Figure 1 Adjusted survival curves based on opium consumption.

DISCUSSION

The current study represents the overall and opium-based stratified survival of patients undergoing CABG surgery who were followed-up for a median time of 78.7 mo. The prevalence of opium addiction was found to be 14.5% in our study. To our knowledge, studies are lacking to clarify the long-term effects of opium consumption on survival of patients undergoing CABG surgery. One of the notable points of our study was relatively long duration of follow-up.

Considering overall survival of patients undergoing CABG surgery, we found an overall survival of 91.8% in 6.5 years (78.7 mo). Five-year survival has been reported 72.1% in Yoo *et al*[21]'s study and Dunning *et al*[22] identified a ten-year survival of 66%. Meanwhile unadjusted 5 and 10-year survivals have been reported 83.8% and 65% in Filardo *et al*[1]'s research.

We identified that age, BMI, EF, diabetes mellitus and cerebrovascular accident could independently and significantly predict all-cause mortality of patients undergoing CABG surgery. Findings of Leavitt *et al*[5], Marcheix *et al*[23] and Barsness *et al*[24] support our results in terms of adverse effect of diabetes mellitus on long-term survival. Interestingly cerebrovascular accident had the greatest HR of 3.45 in predicting mortality by multiple Cox regression analysis suggesting that non-cardiac comorbidities may play an important role in patients' outcomes as well as unfavorable cardiac performance.

We found a significant HR of 0.89 for BMI in predicting overall mortality. Our results were in accordance with

those reported in Gruberg *et al*[25]'s work. They found that overweight or obese patients under CABG have significantly better survival outcomes at 3-year follow-up than those with normal BMI. The phenomenon obesity-mortality paradox which is generally accepted in short term outcome studies is described by better outcome in patients with higher BMI compared to the others. However, there is no consensus in long term investigations as Del Prete *et al*[26] noted that long-term survival was not significantly different between obese and non-obese patients after making adjustment model (HR = 1.2, *P* = 0.2). This is partially explained by increasing rate of complications due to major cardiovascular risk factors and substantial re stenosis in grafted coronary arteries by time[27,28]. Though we followed our patients for long period of time we found that BMI was still a predictor of mortality. Low mortality rate in our cohort compared to other studies with similar time intervals that reflect lower risks and complications in our patients could be an explanation. The other reason may be the finding of missed to follow up in a group of our patients which decreases the median time of overall follow-up.

Opium can potentially cause coronary atherosclerosis and increase cardiovascular mortality in different ways. Some metabolic changes by opium that could have deleterious effects on cardiovascular system include: Decreasing plasma testosterone and estrogen, and increasing plasma prolactin, increasing insulin resistance, increasing inflammation as well as oxidative stress, increasing fibrinogen and factor VII, and decreasing apolipoprotein A, increasing the release of nitric oxide and inhibiting production and release of hydrogen peroxide. Moreover, opium can decrease myocardial oxygenation from different ways that could extend infarct size and increase probability of death[29,30].

The role of opium in CAD remains controversial. Masoomi *et al*[13] showed that opium was an independent risk factor of CAD in non-smoker patients. But findings of Sadeghian *et al*[14]'s research on 4398 isolated CABG patients and opium dependence rate of 15.6%, found no relationship between post CABG in hospital complications and opium addiction. But on the other hand, in a study conducted by Safaii *et al*[15] on 6-mo outcomes of CABG patients, opium usage leaded to more readmission following CABG operation.

We found a HR of 2.1 for mortality in opium consumers as compared to patients who did not use opium with a borderline *P* value of 0.06. Since the rate of smoking is higher among opium-consumers, when we further adjusted the results by smoking, we observed that the role of smoking would be more prominent in predicting mortality so that HR for opium decreased to 1.2. Though our findings are not in favor of any protective role for opium in smoker cardiac patients, there is still no evidence to consider opium as a risk marker for long term survival in this group too.

The main problem with clarifying pure effect of opium on long term outcome in cardiac patients is high co incidence of smoking and opium addiction (Table 2). In deed there were only 15 patients who were opium users and non-smokers in our cohort. We need to perform further investigation to clarify pure effect of opium, because ignoring the adverse effects of opium and attributing any poor clinical outcomes to the smoking alone would be potentially associated with worse consequences.

There are other obstacles to detect the effects of opium on outcome in coronary patients that has been discussed elsewhere[30,31]. Briefly there are variations in self-reported dosage, route of usage, and purity of consumed opium. The other important issue probably would be the reason for beginning opium consumption: recreational or for pain relief[29,30].

In conclusion, in the present study, we found advanced age, low EF, DM and CVA as predictors for long term mortality. However, due to the simultaneous impact of smoking as a confounding variable neither the cardio protective role of opium in ischemic phase suggested in some studies nor its role as a predictor for long-term survival of CABG patients could be justified. Further large sample size studies are needed to clarify pure opium role and verify the aforementioned findings.

COMMENTS

Background

Cardiovascular diseases especially coronary artery disease have been known causes of morbidity and mortality all over the world. Though most of predictive factors of outcome in coronary artery bypass surgery are common among different countries, there are ethnic, environmental, and psychosocial specifications that necessitate separate studies on predictors of outcome in different parts of the world. Opium consumption is a controversial topic with regard to its impact on coronary artery disease outcome. Current literature is not conclusive about short term mortality and there is paucity of data on the role of opium as a risk marker for long term survival after coronary artery bypass surgery.

Research frontiers

A large cohort in normal population revealed that opium consumption has been associated with increased all cause and cardiovascular mortality. Some studies are focused on the pattern of obesity impact on outcome in cardiovascular disease. Finding a mixed group of factors including risk markers and a panel of biomarkers with the highest level of outcome prediction is currently an important research topic.

Innovations and breakthroughs

It is always possible to mix up the role of opium consumption with the known risk of cigarette smoking. This study showed that opium has no protective role in smoker cardiac patients. However, there is still lack of evidence to consider opium as a risk marker for long term outcome in cardiac surgical patients.

Applications

This study showed that advanced age, low ejection fraction, lower body mass index, diabetes mellitus, and cerebrovascular accident (CVA) are predictors for long term mortality. High hazard ratio for CVA put an emphasis on the importance of this non cardiac factor in predicting mortality.

Peer-review

This is an interesting manuscript about the effects of opium consumption on all-

cause mortality in patients undergoing coronary artery bypass graft surgery.

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CASE REPORT

Pulmonary vein thrombosis in a patient with polycythemia vera

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Abstract

Pulmonary vein thrombosis (PVT) is a rarely encountered disease entity with varied clinical presentations. It is usually associated with lung carcinoma, lung surgeries and as a complication of the radiofrequency catheter ablation procedure for atrial fibrillation. Its clinical manifestations can vary from mild hemoptysis to lung infarction with hemodynamic compromise. A 76-year-old male presented with a 2-d history of pleuritic left sided chest pain. His past medical history included polycythemia vera, atrial fibrillation, coronary artery disease, pulmonary embolism and pulmonary hypertension. Chest radiograph was normal, troponins were normal and the 12-lead electrocardiogram did not show any ischemic changes. A computerized tomography pulmonary angiogram revealed a filling defect in the left lower lobe pulmonary vein. He was treated with subcutaneous enoxaparin and his symptoms improved. This case highlights a rare etiology of chest pain and the first reported case of the association of polycythemia vera and pulmonary vein thrombosis. A high index of suspicion is required for appropriate diagnostic work up. PVT can mimic pulmonary embolism. The diagnostic work up and treatment strategies depend on acuity of presentation.

Key words: Pulmonary veins; Polycythemia rubra vera; Thrombosis/etiology; Thrombosis/radiography

Core tip: Pulmonary vein thrombosis (PVT) is a rare but potentially life-threatening disease entity. Its signs and symptoms are often non-specific and it can be difficult to diagnose unless there is a high index of clinical suspicion. Misdiagnosis can lead to grave consequences. We describe a case of PVT in the setting of polycythemia vera. The patient had presented with symptoms of pleuritic chest pain and the workup revealed a thrombus in the left inferior pulmonary vein. This association of polycythemia vera with PVT has not

been reported in the literature previously. The PVT is a less known disease process and with this manuscript, we would like to briefly review its causes, presentation and treatment options.

Bhardwaj B, Jacob D, Sharma A, Ghanimeh MA, Baweja P. Pulmonary vein thrombosis in a patient with polycythemia vera. *World J Cardiol* 2016; 8(11): 684-688 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i11/684.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i11.684

INTRODUCTION

Pulmonary vein thrombosis (PVT) is a rare but potentially life threatening condition. Lung circulation has rich venous collaterals; however certain medical conditions can cause obstruction to the pulmonary veins[1]. The various etiologies for the pulmonary vein thrombosis can be broadly categorized as post lung surgery, from primary or secondary tumors of lung, cardiac causes and miscellaneous causes[2-8]. The clinical diagnosis of the PVT is difficult as its signs and symptoms can be vague and nonspecific. It can either present acutely in the form of dyspnea, pleuritic chest pain and hemoptysis or as progressive lung fibrosis and chronic pulmonary edema[9]. Several different imaging modalities have been used in diagnosing PVT including computerized tomography angiography (CTA), transesophageal echocardiography (TEE) and magnetic resonance imaging (MRI)[8-13]. PVT is managed with anticoagulation but treatments can differ depending on the various etiologies and clinical status on presentation. We are presenting a case of pulmonary vein thrombosis in a patient with polycythemia vera which is the first reported case in literature of this unique association.

CASE REPORT

A 76-year-old male presented with a two day history of the severe left sided chest pain. The chest pain was sudden onset, unrelated to exertion but worsened with inspiration. His past medical history included polycythemia vera, coronary artery disease, pulmonary hypertension, pulmonary embolism, diastolic heart failure and permanent atrial fibrillation. He had JAK2 proven polycythemia vera and had required intermittent phlebotomy in the past. He was on chronic thromboprophylaxis with aspirin. He was on chronic anticoagulation with warfarin due to his history of pulmonary embolism. He was admitted with the suspicion for acute coronary syndrome. His troponins remained within normal limits and there were no significant electrocardiogram (ECG) changes. His ECG revealed an ejection fraction of 55% with grade 2 diastolic dysfunction and elevated pulmonary artery pressures. His labs were within normal limits other than hemoglobin of 12.9 g/dL and elevated white blood cell count of 17400. INR on arrival was 2.1. He underwent a CT angiography with suspicion for pulmonary embolism. CTA revealed a left inferior pulmonary vein thrombosis with extension into the left atrium (Figure 1) along with left lower lobe consolidation. He was immediately started on therapeutic dosage of low molecular weight heparin and antibiotics for the presumed bacterial pneumonia. His symptoms improved on the treatment and he was discharged with subcutaneous low molecular weight heparin. A follow up CT angiogram a few weeks later showed the resolution of his pulmonary vein thrombosis (Figure 2).

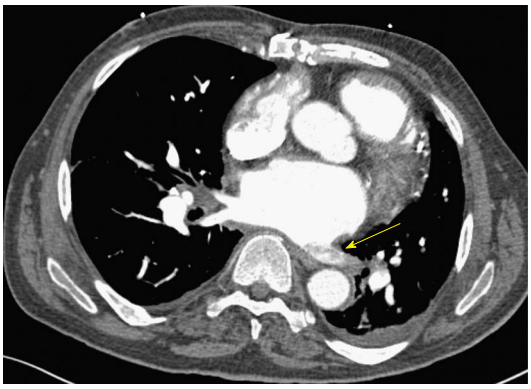

Figure 1 Computerized tomography angiography showing the pulmonary vein thrombosis of the left lower pulmonary vein. A yellow arrow marks the position of the thrombus.

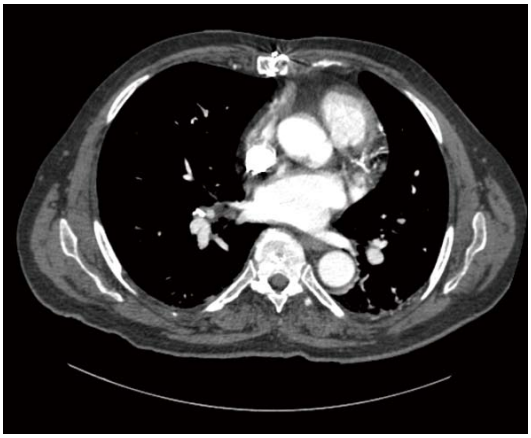

Figure 2 A follow up computerized tomographic angiogram showing the resolution of pulmonary vein thrombosis in the left lower pulmonary vein.

DISCUSSION

Etiologies

Pulmonary vein thrombosis is the most distal source of the upstream arterial thrombi. It is most common etiologies include lung surgeries either in the form of lung transplantation and lobectomies[2,3]. Other etiologies associated with PVT are lung cancers and sclerosing mediastinitis[5,6]. PVT has been associated with atrial myxomas and after radio frequency catheter ablation[7,8] (Figure 3).

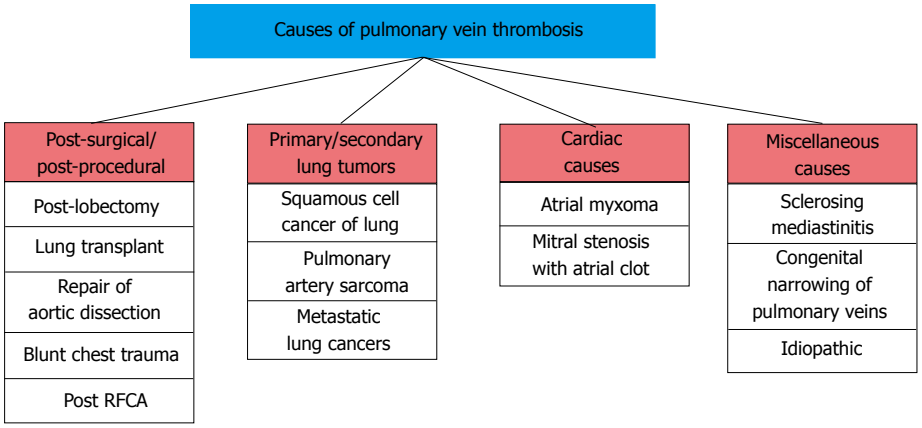

Figure 3 Flowchart describing the various causes of pulmonary vein thrombosis. RFCA: Radio frequency catheter ablation.

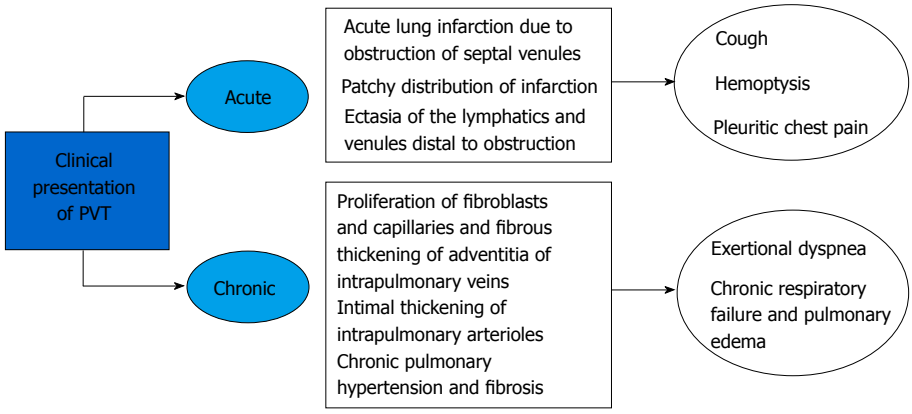

Figure 4 A flow diagram of the two different clinical presentation of pulmonary vein thrombosis. PVT: Pulmonary vein thrombosis.

Clinical presentations

The clinical presentation of the PVT can vary depending on the number of veins involved, extent of occlusion, adequacy of the venous collaterals and degree of lymphatic obstruction (Figure 3). Historically the pulmonary vein thrombosis presentation is associated with a triad of cough, dyspnea and hemoptysis[1]. The clinical presentations can be broadly divided into acute lung infarction pattern with cough, chest pain and pleuritic chest pain or in an insidious symptom pattern with progressive pulmonary fibrosis and pulmonary edema[1,9]. Patients with chronic PVT are prone to recurrent bouts of respiratory infection. In advanced disease with involvement of more than one pulmonary vein, patients can have frequent episodes of pulmonary edema progressing to intractable heart failure[1].

Pathophysiology

Before understanding the pathophysiology of the pulmonary vein thrombosis it is important to know that both pulmonary and bronchial circulation drain into the left atrium through the pulmonary veins. Any obstruction to this flow can lead to dilation of the bronchial and pulmonary veins. The pathophysiology of the symptoms can be very similar to mitral valve stenosis, *i.e.*, increase in pulmonary venous pressure and compensatory pulmonary arterial vasoconstriction leading to increase in right ventricular end diastolic pressures. In an animal study Wyatt *et al*[11] had demonstrated sequential changes in the canine lungs after the ligation of pulmonary veins which comprised of congestion, serum extravasation and alveolar hemorrhage leading to lobar consolidation.

Diagnosis

It is a challenge to establish the diagnosis of the PVT syndrome unless there is a strong clinical suspicion. Several diagnostic modalities can help in making the diagnosis including chest X-ray, CTA[6,7,9], TEE[5,12] or MRI[10] (Figure 4 and Table 1). Chest X-ray may reveal no finding or nonspecific air space disease or opacities[2]. Modified CT angiography that is utilized to identify pulmonary artery embolus can also detect the pulmonary vein thrombosis. ECG gated MRI is the least invasive modality to demonstrate the pulmonary vein embolus extending to left atrium. MRI imaging can also differentiate the bland thrombus from a tumor thrombus[10]. Pulmonary angiography is not commonly used to diagnose PVT due the increased risks from the procedure as well as contrast exposure. A normal

Table 1 Diagnostic modalities used in the diagnosis of pulmonary vein thrombosis with the findings and drawbacks

Type of modality	Findings	Drawbacks
Chest X-ray	Increased vascular marking, increased hilar size Consolidation, atelectasis Mitral configuration of pulmonary conus (extensive PVT)	Nonspecific in the setting of coexistent infections Variable findings
CT angiography/multidetector CT	Longer delays of contrast clearance on the venous phase Filling defect in pulmonary veins	Requires IV contrast Artifact from heart motion, dense contrast, poorly opacified blood can leads the PVT undetected
TEE	Can detect the thrombus when it extends to the left atrium Echo dense thrombus occluding the pulmonary veins	Invasive, requires sedation Can't detect the distal PVT
MRI	Least invasive methods Can differentiate blood clot from tumorous clot	Expensive Needs cooperative patients with stable cardiac rhythm
Pulmonary angiography	Failure to enhance the vein lumen A partial filling defect surrounded by normal contrast	Invasive and requires the contrast exposure Possibility of injury to the pulmonary artery, cardiac perforation, cardiac arrest

PVT: Pulmonary vein thrombosis; CT: Computerized tomography; TEE: Transesophageal echocardiography; MRI: Magnetic resonance imaging.

arterial phase and delayed or absent venous filling during the pulmonary angiogram can demonstrate a pulmonary vein thrombosis[1].

Complications

The PVT can become a source of arterial thromboembolic disease. Because of the high flow in pulmonary venous circulation small fragments of the platelets and fibrinous material can constantly break off from the thrombus. Garcia *et al*[12] described a case of bilateral femoral arterial occlusion in a patient of PVT. It can lead to pulmonary infraction and pulmonary gangrene[1] during the acute occlusive phase and in chronic phases it can cause progressive pulmonary fibrosis[9]. There are case reports about PVT complicating old myocardial ischemia[13].

Treatments

There is no clear consensus regarding the treatment of the PVT. The choice of therapy depends on the clinical status of the patient and the etiology of PVT. In case of pulmonary infraction requiring urgent intervention, surgical treatments in the form of embolectomy or lung resection might be indicated[2,14]. Appropriate use of the anticoagulation in the absence of hemorrhage can prevent clot progression and embolization. In patients where any carcinoma is involved, the use low molecular weight heparin is advisable. In the past, antibiotics were used for treating PVT[11,14]. But the role of antibiotics in the absence of infection is questionable. The use and duration of the Warfarin for PVT has not been evaluated in studies. In patients with PV, the risk of thrombosis directly correlates with hematocrit, and frequent phlebotomies to maintain this at < 45% in males and < 42% females remains the cornerstone of therapy for all patients groups. The venous thrombotic events are managed in standard fashion with parenteral heparin followed by oral anticoagulation with warfarin. The patients should be followed closely with strict monitoring of the INRs and platelet counts as the patients are at increased risk for bleeding too. Systemic anticoagulation might not be sufficient and these patients should get concomitant myelosuppressive therapy preferable with hydroxyurea as well as phlebotomies. In a study done by De Stefano *et al*[15] cytoreductive therapy reduced the incidence of rethrombosis by 50% especially in patients who presented with acute coronary syndrome. The use of systemic anticoagulation (after venous thromboembolism) as well as antiplatelet therapy (after cerebrovascular accidents as well as venous thromboembolism) improved the protective effect. It is recommended to use the cytoreductive chemotherapies in addition to phlebotomies in high risk patients (age > 60 years and previous thrombotic events)[16].

In our patient pulmonary venous thrombosis occurred while he was on both aspirin and warfarin with a therapeutic INR of 2.1. It was considered to be warfarin failure and his anticoagulation was changed to subcutaneous enoxaparin while continuing low dose aspirin.

In summary, we want to describe a case of pulmonary venous thrombosis in a patient with polycythemia vera. The clinical signs and symptoms of PVT can mimic pulmonary arterial embolism, acute coronary syndrome or pulmonary infections. Early recognition is imperative as PVT can lead to numerous complications including arterial thromboembolic disease. Anticoagulation can be chosen as first line therapy if there are no contraindications. Choice of anticoagulant agent can be tailored based on the clinical picture and patient comorbidities. In our case the patient developed thrombosis despite being on warfarin and was discharged on low molecular weight heparin. Cytoreductive therapies reduce the recurrence of the thrombotic events and should be considered in all high risk patients. Further studies and experience is needed to make the correct decision about the type and duration of anticoagulation in patients with PVT.

COMMENTS

Case characteristics

This is a unique case describing a rare presentation of polycythemia vera as a thrombotic event in pulmonary veins.

Clinical diagnosis
The patient presented with a left sided chest pain and the computerized pulmonary angiogram revealed a thrombus in the left lower pulmonary vein.

Differential diagnosis
Coronary artery disease, pulmonary embolism and pneumonia.

Laboratory diagnosis
The INR on arrival was 2.1, white cell count of 17400 and computerized tomographic angiogram revealed a thrombus on the left lower pulmonary vein.

Imaging diagnosis
A filling defect on the venous phase of the computerized pulmonary angiogram which diagnosed a thrombosis of the left lower pulmonary vein.

Treatment
Patient was started on low molecular weight heparin. He was on warfarin and had a therapeutic INR when he presented with the pulmonary vein thrombosis. A computerized tomography angiography done few weeks later showed resolution of the thrombus.

Related reports
Pulmonary vein thrombosis is an uncommonly encountered disease entity with various clinical presentations. It can lead to serious complications including lung infarction and hemodynamic instability. Although polycythemia vera presents with thrombosis at unusual sites but the association of pulmonary vein thrombosis with polycythemia vera has not been described in the literature so far.

Term explanation
Computerized tomographic pulmonary angiography is a common modalities utilized to rule out acute pulmonary embolism. It utilizes infusion of an iodinated contrast to look at the pulmonary vasculature.

Experiences and lessons
The timely diagnosis of pulmonary vein thrombosis could be difficult and requires high index of suspicion. It should be considered an etiology for the clinical presentations with chest pain and dyspnea in people at high risk for thrombotic events.

Peer-review
A well described case of pulmonary vein thrombosis presenting as left sided chest pain. In the discussion authors have delineated the spectrum of clinical presentation and treatment options in detail. The type and duration of anticoagulants use for the pulmonary vein thrombosis has not been studied in clinical trials so far.

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