The vulnerable plaque: From plaque instability towards thrombus instability

Li, Xiaofei

Link to publication

Citation for published version (APA):
Li, X. (2014). The vulnerable plaque: From plaque instability towards thrombus instability

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)

Download date: 22 Dec 2018
Distal embolization of hydrophilic coating material from coronary guide wires after percutaneous coronary interventions

Maik J. Grundeken, MD¹, Xiaofei Li, MD², C. Eline Kurpershoek, MD², Miranda C. Kramer, MD¹, PhD, Aryan Vink, MD, PhD³, Jan J. Piek, MD, PhD¹, Jan G.P. Tijssen, PhD¹, Karel T. Koch, MD, PhD¹, Joanna J. Wykrzykowska, MD, PhD¹, Robbert J. de Winter, MD, PhD¹, Allard C. van der Wal, MD, PhD²

Heartcenter, Academic Medical Center – University of Amsterdam, Amsterdam, The Netherlands
Department of pathology, Academic Medical Center – University of Amsterdam, Amsterdam, The Netherlands
Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands

Submitted
Chapter 9

Abstract

Background
Coronary guide wires are indispensable during percutaneous coronary interventions (PCI). Nowadays, most guide wires have hydrophilic coatings to improve their trackability, allowing easy lesion passage, and facilitating balloon and stent positioning. Recent reports however have raised concerns about detachment and subsequent embolization of these hydrophilic coatings.

Methods and results
We have retrospectively reviewed histological samples of the myocardium, obtained during autopsies in the period 2009-2013, from all patients who had a history of PCI (n=40). Foreign material was observed in the distal myocardium in 4 patients (10%). Furthermore, we have reviewed 205 thrombus specimen which were obtained during thrombus aspiration in the setting of primary PCI in the period 2005-2009. In 45% of the cases foreign material was observed within the thrombus. Finally, we have examined the histopathological appearance of hydrophilic guide wire coating material ‘ex-vivo’ by embedding the coating in placenta specimen and cut and stain it in exactly the same manner as the myocardium and thrombus specimen. The histopathological appearance of the hydrophilic coating ‘ex-vivo’ was identical to the foreign material found ‘in-vivo’.

Conclusions
Distal embolization of hydrophilic coating material was observed in 10% of the patients who had a history of PCI. Hydrophilic coating material was found in 45% of coronary thrombus specimen obtained during thrombus aspiration. These findings suggest that detachment and distal embolization of hydrophilic coating material from coronary guide wires occurs more often than the sparse literature on this topic suggests.
Introduction

Coronary guide wires are indispensable in the daily armamentarium of the interventional cardiologist during percutaneous coronary interventions (PCI). Guide wires are needed during PCI to track through the coronary vessels, to access and cross lesions, and to provide support for interventional devices. Whereas Andreas Grüntzig used a short guide wire attached to the tip of a blunt inner balloon catheter with a closed-end during the first angioplasty,\(^1\) Simpson et al. reported the first use of an over-the-wire balloon system with an independently movable guide wire with a flexible tip.\(^2\) The technology of coronary guide wires has been developed rapidly ever since. One such development was to coat the guide wire with a hydrophilic coating. Hydrophilic coatings attract water and need lubrication before insertion. After the coating contacts with liquids it becomes a slippery gel-like surface. This provides a lubricious, low friction feel inside the vessel and improves the trackability of the guidewire and subsequent positioning of balloons and stents.

Recent reports have suggested that these hydrophilic coatings can detach from the wire and can embolize distally in the microvasculature of the myocardium\(^3\)\(^-\)\(^7\) Although these reports only described a very limited number of patients, similar findings have been reported related to other vascular procedures in which hydrophilic coated materials were used. Such reports include neuro-interventional procedures and percutaneous procedures of the lower extremities, in which embolized foreign materials were found in the microvasculature of the lower extremities, brains and lungs during histopathological evaluation of biopsies or at autopsy.\(^8\)\(^-\)\(^11\) Whether this low number of reports reflects a truly low incidence of these distal embolizations of foreign material, or whether these embolizations occur more often yet are under recognized, is uncertain.

We performed histological examination of 200 thrombus aspirates to evaluate how often hydrophilic coatings liberate from guide wires. All these thrombus samples were retrieved with thrombus aspiration from the sites of coronary culprit lesions in the setting of primary PCI for the treatment of patients presenting with ST-segment elevation myocardial infarction (STEMI). To confirm whether or not these foreign materials indeed embolize to the distal microvasculature, we reviewed samples from the myocardium which were obtained during routine autopsies of patients who had a history of PCI. Finally, to confirm the source of the foreign material emboli, we examined the histopathological appearance of the hydrophilic coating of the guide wire most commonly used in our center and compared the histology with that of the material observed in the thrombus specimen obtained from thrombus aspirations.
Chapter 9

Methods

Setting

Our center, the Academic Medical Center in Amsterdam, The Netherlands, is a large referral hospital with an annual PCI volume of ~2000 procedures, 600 of which are primary PCIs. Primary PCI is performed in accordance with standard guidelines on ST-segment elevation myocardial infarction (STEMI) treatment and myocardial revascularization. The Hi-torque (HT) Balance Middleweight (BMW) Universal (Abbott Vascular, Santa Clara, USA) was the ‘workhorse’ coronary guide wire in our institution. Other coronary guide wires used were the HT Floppy (Abbott Vascular, Santa Clara, USA), the HT Pilot 50 (Abbott Vascular, Santa Clara, USA), the HT Whisper (Abbott Vasulcar, Santa Clara, USA), the HT Extra S’port (Abbott Vascular, Santa Clara, USA), and the Crosswire (Terumo, Tokyo, Japan). Guidewire selection was at the discretion of the operator. Thrombus aspiration has been part of the clinical routine during primary PCI in our center since August 2001. Two different thrombectomy devices have been used during the study period: the 6F Export aspiration catheter (Medtronic Vascular Inc, Santa Rosa, USA), which became available in August 2004; and the 6/7F Proxis embolic protection device (St Jude Medical, St Paul, USA), which became available in February 2004. The choice of thrombectomy device was at the discretion of the operator. Thrombus material retrieved was fixed in formalin immediately after thrombus aspiration and brought to the department of cardiovascular pathology. The material was embedded in paraffin and processed for histology, after it has been fixated for 24 hours. Serial sections of 5 μm were cut and mounted on glass slides and stained with hematoxylin and eosin (H&E) and elastic von Gieson (EvG). 12, 13

Evaluation of thrombus material and guide wires used

We retrospectively evaluated 205 thrombus specimen from 205 different patients from thrombus material obtained from December 1, 2005 until March 31, 2009. All thrombus specimen were classified for the presence or absence of foreign material. This assessment was performed by an investigator being unaware of the type of guide wire used during primary PCI.

Hereafter, the procedural records from the PCI procedures were obtained and the type of guide wires used was extracted. Most often one wire was used for lesion crossing and thrombus aspiration. If more than one type of guide wire was mentioned in the procedural record, the first mentioned was used for the current analysis, since we assumed that the first-recorded guide wire was used during thrombus aspiration, while the subsequent recorded guide wires were likely to be used for subsequent balloon-dilations and stent placements.
Differences in occurrence of foreign material was compared among the three guide wires used most in the study period (December 1, 2005 - March 31, 2009) by using Chi-square statistics. Furthermore, we have performed an univariable and multivariable logistic regression analysis to adjust for potential lesion-based confounding factors. Variables associated with observed foreign material by univariable analysis (p<0.2), were entered in the multivariable model. A P-value <0.05 in the multivariable analysis was considered statistically significant.

Evaluation of myocardial embolization
Post-mortem coronary angiograms of autopsy patients between 2009 and 2013 were screened for the presence of intra-coronary stents at the department of Pathology of the Academic Medical Center. Histological samples from the myocardial territory of the stented coronary vessel were retrospectively reviewed for the presence of foreign material from all patients with stents visible on the post-mortem angiograms. Myocardial samples were obtained during routine clinical autopsies. These routine clinical autopsies were performed according to the following local standard autopsy protocol: First, permission for the autopsies was obtained from relatives of the deceased patients. After gross inspection, coronary arteries were carefully dissected en bloc from the epicardial surface of the heart, and decalcified in EDTA for 4 days. All coronary segments containing visible lesions in corresponding postmortem angiograms were cut in 3-mm segments, and, after routine processing, embedded in paraffin. Myocardial ischaemia was assessed by means of Nitro Blue Tetrizolium staining of a fresh transversal biventricular slice at the mid-papillary level of the heart. Decolorization of grossly normal appearing myocardium was interpreted as recent-onset ischaemia. Three sections were randomly taken from the myocardial territory of each of the three major epicardial vessels and stained with H&E and EvG. All available myocardial sections were evaluated for the presence of embolized hydrophilic coating.

Histopathological conformation of the source of the hydrophilic coating
To attempt to determine the source of the foreign material emboli in the myocardium and the foreign material seen in the thrombus specimen, we examined the histopathological appearance of the hydrophilic coating of the guide wire most commonly used in our center. A steel blade was used to scrape off the polymer coating from the most often used (‘work-horse’) guide wire in our center (HT BMW Universal II, Abbott Vascular, Santa Clara, USA). In order to be able to properly cut these coatings, they were embedded in placenta specimen. These placenta specimen where then processed in the same manner as the obtained thrombus material: after embedding in paraffin,
serial sections of 5 μm were cut and mounted on glass slides and stained with H&E. The embedded hydrophilic coating in these cross sections were then visually compared with the foreign material found in the thrombus specimen.

Results

Autopsies

Coronary stents were identified on post-mortem coronary angiograms in 40 hearts from a total of 511 autopsy patients (7.8%). Fourteen patients received stent implantation within 6 months prior to the autopsy. Nineteen patients had an interval longer than 6 months between PCI and autopsy. The intervals are unknown for 7 patients. Embolization of hydrophilic coating in the distal myocardium was observed in 4 cases (10%). The interval from PCI until autopsy in these four patients was 1, 1, 5 and 3641 days, respectively. Distal embolization was more frequently observed in patients with recent stent implantation (<6 months) than in patients with a longer interval (>6 months) from PCI until autopsy (21% vs 5%, respectively). The 4 patients in whom distally embolized foreign material was found are described in detail below.

The first case was a 70-year old male patient with an acute anterior myocardial infarction who was treated with PCI of the proximal left anterior descending (LAD) and the ramus circumflex (RCx) arteries. The LAD was wired with a BMW Universal II guide wire and treated with a 3.0x15mm drug-eluting stent (DES). Hereafter, the RCx was wired with a Pilot 50 guide wire treated with a 2.5x15mm DES. There were no technical problems during PCI. The patient developed pulseless electrical activity and died soon thereafter. Autopsy revealed a recent transmural infarction of the septum and the lateral wall as the most likely cause of death. Furthermore, microscopy of the samples taken from the myocardium identified amorphous, light-basophilic, non-refractile, and non-polarizable material behind the stent struts, where it was encapsulated in fresh thrombus (figures 1A-1C). Material with similar appearance was also found in small, distal intramural arteries (figures 1D and 1E).

Case 2 was a 73-year old male who presented with hemodynamic instability caused by an anterior myocardial infarction based on a thrombotic occlusion of the proximal LAD. A primary PCI was performed. Thrombus aspiration was performed, although no thrombus material was retrieved. Hereafter, a 3.5x28mm BMS was implanted. Despite satisfactory angiographic result, the patient was still in cardiogenic shock and died 5 days later due to end-stage heart failure. Microscopic evaluation of myocardial samples showed amorphous, non-refractile, non-polarizable foreign material in small arteries of the myocardium (figures 1F and 1G).
Case 3 was a 70-year old male patient presenting with STEMI based on a stent thrombosis (ST), 3 months after treatment of a subtotal lesion in the RCx treated with a 3.5x28mm bio-reabsorbable vascular scaffold. After wiring with a BMW Universal II guide wire, thrombus aspiration was performed which could not retrieve thrombotic material. Reperfusion of the RCx was obtained after balloon dilatations. Despite the achieved reperfusion, the patient died one day later due to hemodynamic instability based on heart failure caused by the acute infarction. Myocardial samples showed
thrombus around the stent struts with amorphous foreign material embedded within this thrombus (figures 1H and 1I). In addition to diffuse reperfusion injury, the distal myocardium showed multiple locations of embolization of the same foreign material as seen within the intracoronary thrombus (figures 1J-1L).

Case 4 was a 73-year old male patient with a history of coronary artery bypass graft surgery (CABG) 20 years earlier and nine PCIs (of which the last PCI was 10 years before his death). Furthermore, he underwent transcatheter aortic valve implantation 10 days before his death. The patient died due to sepsis, which was most likely caused by an acute necrotizing cholecystitis. Microscopy of myocardial samples showed intravascular amorphous, non-refractile, and non-polarizable material (figures 1M and 1N).

**Hydrophilic coating material in thrombus aspiration specimen**

Thrombectomy samples from 205 PCI patients were reviewed. The HT BMW Universal was the most used guidewire during thrombus aspiration in the study period (144 cases; 70%), followed by the HT floppy (7.8% of the cases), the HT Whisper (3.4%), the HT Extra S’port (1.5%), and the Crosswire (0.5%). In 34 cases (17%), the used guidewire could not be retrieved from the PCI reports.

Foreign material was observed in 92 of the 205 thrombus sections evaluated (45%). From the three most frequently used guide wires, foreign material was most often observed in cases in which the HT Whisper was used (71% of the thrombus sections).

![Figure 2. Differences in the frequency of foreign material in thrombus specimen found between the three most used coronary guide wires. BMW: balance middle weight. HT: high-torque.](image-url)
Distal embolization of guidewire coating after PCI

contained foreign material), followed by the HT BMW Universal (46%). Foreign material was least often observed when the HT Floppy was used (19%). The differences among these three groups were statistically significant (p-value for trend 0.040, see figure 2). The percentage of observed foreign material in the group with unknown guidewire (47%) was comparable with the whole group (45%). Adjusted for potential lesion-based confounders (lesion location and PCI indication), guide wire type used was still associated with the observation of foreign material in the thrombus specimen (see online table 1).

**Histopathological conformation of the source of the hydrophilic coating**

Figure 3 shows representative examples of foreign material found in thrombus sections (left panels 3A - 3F). The hydrophilic coating on the polymer which is scraped off from a HT BMW Universal II guide wire, displayed in the right panels (3G - 3L), has a similar appearance compared with the foreign material found in the thrombus specimen.

![Histopathological appearance of hydrophilic guide wire coating. Left panels (3A - 3F) show examples of foreign material found in thrombus specimen obtained from coronary thrombus aspiration. Right panels (3G - 3L) show polymer with hydrophilic coating from a balance middle weight guide wire embedded in placenta specimen. Pm: polymer coverage. Note the similarity between the foreign material found in the thrombus specimen and the hydrophilic coating on the polymer guide wire cover (black arrows).](image-url)


Chapter 9

Discussion

The most important findings of the current study are:

hydrophilic coating material was found in almost half of the coronary thrombus specimen examined, suggesting detachment of this coating from guide wires during thrombus aspiration;

the frequency of occurrence of these coating detachments was different between the different guide wires used;

hydrophilic coating material was found in at least 10% of deceased patients undergoing autopsy who had a past medical history of PCI, in one patient 10 years after the last PCI procedure;

We have confirmed the hypothesis that the foreign material detaches from coronary guide wires by comparing the ‘in-vivo’ histopathological appearance with the histopathological appearance of guide wire coatings ‘ex-vivo’, showing an identical appearance. These findings suggest that distal embolization of hydrophilic coatings occurs much more frequently than the sparse literature on this topic suggests.

Previous reports

To our knowledge, distal embolization of foreign material in the myocardium after PCI has only been reported in five previous case reports. The first report we found described a 77-year female who experienced an acute myocardial infarction for which she underwent PCI with stent placement in the right coronary artery (RCA) and the ramus circumflex artery (RCx). Two weeks later she suffered from a fatal arrhythmia. Autopsy revealed multiple basophilic, amorphous, focally lamellated, focally granular material in the microvasculature of the myocardium with an inflammatory component consisting of giant cells and lymphocytes. Another case report described multiple intravascular foreign bodies found in the myocardium of a heart transplantation patient who underwent 32 PCIs in the past. These non-refractile, non-polarizable foreign bodies were thought to be derived from the hydrophilic coating of the guide wires used. In a third report, 2 cases were described in which distal embolization of foreign material was observed after recent PCIs. To determine the source of this material, the authors examined the histopathological appearance of the guide wire used and the authors concluded that the hydrophilic coating of this material must have been the source of these embolizations. A fourth report described a case of a 58-year old man who died during PCI of the RCA and RCx due to fatal arrhythmia caused by an evolving myocardial infarction. On autopsy, cylindrical, coiled, basophilic material was seen in the myocardium of the antero-lateral wall. The last report we found described a 65-year old man who died one month after PCI of the RCx. Autopsy revealed
multiple basophilic filamentous to amorphous granular material with an inflammatory giant cell response within the myocardial territory of the ramus circumflex artery. This foreign material could not be identified in other areas of the heart.\cite{7}

There is also some literature available on distal embolization of hydrophilic material in other tissue than the myocardium. A report by Mehta et al. described 9 patients in whom embolized foreign material was found during histopathological examination of biopsies and autopsies.\cite{9} They found distal embolization of foreign bodies to the brain, lungs, and foot. All patients had a history of intravascular medical device use including central venous catheterization, coronary catheterization, lower extremities catheterization, hemodialysis, and intravenous pacemaker implantation. The authors have examined the microscopic appearance of these medical devices showing similarities with the foreign material found in the patients. In another case series, describing 4 neuro-interventional procedures using an infusion microcatheter, autopsy sections revealed intravascular foreign substances suggesting to be derived from the coating of the microcatheters.\cite{10} Another report has described embolization of hydrophilic coating material of a central venous catheter to the lung resulted in multiple cavitating angiocentric granulomatous pulmonary nodules, proven by histopathology of an open lung biopsy procedure, and clinically mimicking a vasculitis.\cite{14} In conclusion, multiple case reports and small case series have demonstrated the occurrence of distal embolization of hydrophilic coating material from medical devices. However, until now studies are lacking which have evaluated the occurrence of distal embolization of hydrophilic coating in a more systematic manner.

**True incidence of distal embolization of foreign material**

The above-mentioned reports have in common that the observation of the intravascular foreign material was a coincidental finding during regular autopsies or biopsies taken for routine clinical practice. The sparseness of these reports might imply that embolization of hydrophilic coatings is an uncommon problem. However, recognizing this foreign material is difficult since it is often described as non-refractile and therefore easily overlooked. The incidence of distal embolization of coating material we found in our autopsy patients with a history of PCI was 10%. Due to the retrospective evaluation of the myocardial samples, using three randomly selected samples from the myocardial territory of each coronary artery during routine autopsy, we believe that the true incidence of distal embolization after PCI is likely higher than 10%. Indeed, we found detachment of hydrophilic coating in 45% of the cases during thrombus aspiration, which is at least suggestive for a higher than 10% incidence of distal embo-
lization of these hydrophilic coatings. To find the true incidence of distal embolization, a prospective study is needed in which the myocardium of patients with a history of PCI is extensively sampled.

**Differences between guide wire types**

We have compared how often foreign material was observed in thrombus specimen between the three most commonly used guide wires (figure 4). The differences observed might be explained by the extent of polymer coverage. Figure 4 shows schematic drawings of the used guide wires showing differences in polymer coverage, with the HT Floppy having no polymer coverage, the BMW Universal having partial polymer coverage, and the HT Whisper having total polymer coverage (polymer in blue, hydrophilic coating in purple). We demonstrated that the guide wire which is completely polymer-covered (i.e. the HT Whisper) was associated with the most frequent

![Schematic drawing of guide wires](image)

**Figure 4.** Schematic drawing of the three guide wires most used during the study period. Figures 1A-1C show schematic drawings of the most distal ~30cm of coronary guide wires most used during the study period. Figure 1A shows the high-torque (HT) Whisper guide wire, with its core-to-tip design. Notice that the distal part of this wire is completely polymer-covered (polymer in blue, hydrophilic coating in purple). Figure 1B shows the HT Balance Middle Weight (BMW) Universal II, with its shaping ribbon design. Notice that this wire is also polymer covered (in blue), except for its coiled tip (hydrophilic coating in purple). Figure 1C shows the HT Floppy wire, also with a shaping ribbon, which does not have any polymer coverage, but with a coil over its entire distal 30 cm (hydrophilic coating in purple).
retrieval of foreign material in the thrombus specimen, while the guide wire without any polymer coverage (i.e. HT floppy) showed to have the least foreign material retrieved during thrombus aspiration. These findings are suggestive that the hydrophilic coating may adhere better if it is attached to the metal of the guide wire directly (as it is completely the case of the HT Floppy) instead of being adhered to a polymer cover.

Clinical implications
At present, the clinical consequences associated with embolization of hydrophilic coating material from coronary guide wires, both in stable angina patients and in patients undergoing primary PCI for STEMI, remain to be elucidated. The fact that one of our patients survived 10 years suggests that the clinical consequences may be limited. Apparently, foreign material can remain in the myocardium for years. However, one might speculate on the other hand that occlusion of small intramyocardial arteries by foreign bodies will lead to impaired cardiac function due to micro-infarctions. Chronic inflammation with presence of eosinophilic granulocytes as a reaction on the foreign material might further attribute to the myocardial impairment. Although distal embolization during PCI is usually clinically attributed to athero-emboli and/or thrombo-emboli from the culprit lesion, it might be attributable to iatrogenic embolization of hydrophilic coating in some of the cases. One might even further speculate that detached hydrophilic coating materials can adhere to previously placed stents, and thereby inducing stent thrombosis, since two of our autopsy patients had coating material encapsulated in thrombus in close proximity of stent struts. Most contemporary large clinical trials do not record the exact type of guide wires used during the procedure. As a consequence, in general, data regarding guide wire type used is lacking which can be used to investigate the relationship between different guide wires and clinical outcomes. Therefore, we believe guide wire type should be captured in the datasets of future clinical trials.

Limitations
A first limitation is that we did not prospectively collect the guide wires used during thrombus aspiration. Therefore, we are not completely certain whether the first mentioned guide wire in the PCI report was indeed used for the thrombus aspiration. Furthermore, from the 205 evaluated thrombus specimens, type of guide wire used was unknown in 17% of the cases. However, as mentioned before, most clinical databases used for contemporary clinical trials do not include guide wire type as variable. Another limitation is that the current data cannot be used to investigate the clinical consequences of distal embolization of hydrophilic coating. Large dedicated
registries capturing used guide wire types are needed to investigate if such relationship exists. Finally, sheets and guiding catheters also have hydrophilic coatings, so other sources for the detachment and embolization of hydrophilic coating material cannot be excluded.

Conclusions
Distal embolization of hydrophilic coating material in the myocardial microvasculature was observed during autopsy in 10% of the patients who had a history of PCI. In 45% of the thrombus specimen obtained with thrombus aspiration during primary PCI, hydrophilic coating material was found within the thrombus. These findings suggest that distal embolization of hydrophilic coatings occurs more often than the sparse literature on this topic suggests. Prospective autopsy studies are needed using a more systematic approach of myocardial sampling to investigate the true incidence of distal embolization of hydrophilic coatings. Furthermore, large clinical trials and registries should capture guide wire type as a variable in their dataset to explore whether embolization associated with certain guide wire types have clinical impact. This information is necessary to evaluate whether the benefits of hydrophilic coatings in terms of guide wire passage and trackability outweighs the potential harm done by the distal embolization of detached coating material.

Disclosures
J.J. Wykrzykowska receives consultancy fees from Abbott Vascular. J.J. Piek is a member of the Medical Advisory Board of Abbott Vascular. The AMC Heartcenter received a restricted research grant from Abbott Vascular. The other co-authors have no conflicts of interest to declare.
References