Percutaneous coronary interventions of bifurcation lesions
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Chapter 3

Distal embolization of hydrophilic-coating material from coronary guidewires after percutaneous coronary interventions

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ABSTRACT

Background
Coronary guidewires are indispensable during percutaneous coronary interventions. Nowadays, most guidewires 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 the histological samples of the myocardium, obtained during autopsies in the period 2009 to 2013, from all patients who had a history of percutaneous coronary interventions (n=40). Foreign material was observed in the distal myocardium in 4 patients (10%). Furthermore, we have reviewed 205 thrombus specimens which were obtained during thrombus aspiration in the setting of primary percutaneous coronary interventions in the period 2005 to 2009. In 45% of the cases, foreign material was observed within the thrombus. Finally, we have examined the histopathologic appearance of hydrophilic-guidewire 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 histopathologic 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 percutaneous coronary interventions. 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 guidewires occur more often than the sparse literature on this topic suggests.
INTRODUCTION

Coronary guidewires are indispensable in the daily armamentarium of the interventional cardiologist during percutaneous coronary interventions (PCI). Guidewires are needed during PCI to track through the coronary vessels, to access and cross lesions, and to provide support for interventional devices. Whereas Gruntzig \(^1\) used a short guidewire attached to the tip of a blunt inner balloon catheter with a closed-end during the first angioplasty, Simpson et al \(^2\) reported the first use of an over-the-wire balloon system with an independently movable guidewire with a flexible tip. The technology of coronary guidewires has been developed rapidly ever since. One such development was to coat the guidewire 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 limited number of patients, similar findings have been reported to be related to other vascular procedures in which hydrophilic-coated materials were used. Such reports include neurointerventional 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 histopathologic 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 guidewires. 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. To confirm whether 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 histopathologic appearance of the hydrophilic coating of the guidewire most commonly used in our center and compared the histology with that of the material observed in the thrombus specimen obtained from thrombus aspirations.
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 treatment and myocardial revascularization. The Hi-torque (HT) Balance Middleweight (BMW) Universal (Abbott Vascular, Santa Clara, CA) was the workhorse coronary guidewire in our institution. Other coronary guidewires used were the HT Floppy (Abbott Vascular), the HT Pilot 50 (Abbott Vascular), the HT Whisper (Abbott Vascular), the HT Extra S’port (Abbott Vascular), and the Crosswire (Terumo, Tokyo, Japan). Guidewire selection was at the discretion of the operator. Thrombus aspiration has been a 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, CA), which became available in August 2004, and the 6/7F Proxis embolic protection device (St. Jude Medical, St. Paul, MN), 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 and elastic von Gieson.

Evaluation of Thrombus Material and Guidewires Used
We retrospectively evaluated 205 thrombus specimens from 205 different patients from thrombus material obtained from December 1, 2005, to March 31, 2009. All thrombus specimens were classified for the presence or absence of foreign material. This assessment was performed by an investigator being unaware of the type of guidewire used during primary PCI. Because thrombus aspiration and histopathologic processing of the obtained thrombus material were all part of daily clinical routine, no formal Institutional Review Board approval was required, according to local rules and regulations.

Hereafter, the procedural records from the PCI procedures were obtained and the type of guidewires used was extracted. Most often, 1 wire was used for lesion crossing and thrombus aspiration. If >1 type of guidewire was mentioned in the procedural record, the first mentioned was used for the current analysis because we assumed that the first-recorded guidewire was used during thrombus aspiration, whereas the subsequent recorded guidewires were likely to be used for subsequent balloon dilations and stent placements.
Differences in occurrence of foreign material were compared among the 3 guidewires used most during the study period (December 1, 2005, to March 31, 2009).

**Evaluation of Myocardial Embolization**

Postmortem coronary angiograms of autopsy patients between 2009 and 2013 were screened for the presence of intracoronary 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 postmortem 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 into 3-mm segments, and after routine processing, they were embedded in paraffin. Myocardial ischemia was assessed by means of nitroblue tetrazolium staining of a fresh transversal biventricular slice at the midpapillary level of the heart. Decolorization of grossly normal-appearing myocardium was interpreted as recent-onset ischemia. Three sections were randomly taken from the myocardial territory of each of the 3 major epicardial vessels and stained with hematoxylin and eosin and elastic von Gieson. All available myocardial sections were evaluated for the presence of embolized hydrophilic coating.

**Histopathologic 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 histopathologic appearance of the hydrophilic coating of the guidewire most commonly used in our center. A steel blade was used to scrape off the polymer coating from the most often used (workhorse) guidewire in our center (HT BMW Universal I; Abbott Vascular). To be able to properly cut these coatings, they were embedded in placental specimen. These placental specimens were then processed in the same manner as the obtained thrombus material: after embedding in paraffin, serial sections of 5μm were cut and mounted on glass slides and stained with hematoxylin and eosin. The embedded hydrophilic coating in these cross-sections were then visually compared with the foreign material found in the thrombus specimen.
Statistical Analysis
Differences in occurrence of foreign material were compared among the 3 guidewires used most by using χ2 statistics. Differences in occurrence of observed foreign material in the myocardium found on autopsy were compared according to the timing from PCI (before or after 6 months) by Fisher exact test because of the low numbers (4 in total). Statistical analyses were performed using the SPSS software package (version 21.0; IBM, Chicago, IL).

RESULTS
Autopsies
Coronary stents were identified on postmortem coronary angiograms in 40 hearts from a total of 511 autopsy patients (7.8%). Fourteen patients received stent implantation within 6 months before the autopsy. Nineteen patients had an interval >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 4 patients was 1, 1, 5, and 3641 days, respectively. The distal embolization rate was numerically higher in patients with recent stent implantation (<6 months) from PCI until autopsy (21% versus 5%), although this was not statistically significant (P value with Fisher exact test: 0.288). 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 and the ramus circumflex (RCx) arteries. The left anterior descending was wired with a BMW Universal II guidewire and treated with a 3.0×15-mm drug-eluting stent. Hereafter, the RCx was wired with a Pilot 50 guidewire treated with a 2.5×15-mm drug-eluting stent. There were no technical problems during PCI. The patient developed pulseless electric 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 images of the samples were taken from the myocardium-identified amorphous, light-basophilic, nonrefractile, and nonpolarizable material behind the stent struts, where it was encapsulated in fresh thrombus (Figure 1A-1C). Material with similar appearance was also found in small, distal intramural arteries (Figure 1D and 1E).

Case 2 was a 73-year-old male patient who presented with hemodynamic instability caused by an anterior myocardial infarction based on a thrombotic occlusion of the proximal left anterior descending. A primary PCI was performed. Thrombus aspiration was performed, although no thrombus material was retrieved. Hereafter, a 3.5×28-mm bare metal stent was implanted. Despite satisfactory angiographic results, the patient
was still in cardiogenic shock and died 5 days later because of end-stage heart failure. Microscopic evaluation of myocardial samples showed amorphous, nonrefractile, non-polarizable foreign material in small arteries of the myocardium (Figure 1F and 1G).

Case 3 was a 70-year-old male patient presenting with ST-segment–elevation myocardial infarction based on a stent thrombosis (ST) 3 months after treatment of a subtotal lesion in the RCx treated with a 3.5×28-mm biodegradable vascular scaffold. After wiring with a BMW Universal II guidewire, thrombus aspiration was performed which could not retrieve the thrombotic material. Reperfusion of the RCx was obtained after balloon dilatations. Despite the achieved reperfusion, the patient died 1 day later because of hemodynamic instability based on heart failure caused by the acute infarction. Myocardial

![Figure 1. Microscopic findings of foreign material emboli in 4 different cases. A–E, Histopathologic findings during autopsy of a 70-year old male patient described in the text. A, A large intrastent thrombus. The 2 black squares in (A) are indicating (B) and (C) which show foreign material behind the stent struts encapsulated in thrombotic material. D and E, Foreign material in the microvasculature of the myocardium of the same patient (A, 2× zoom; B–E, 40× zoom). F and G, Histopathologic findings of the second autopsy case showing embolized foreign material in the microvasculature of the myocardium (black square in F [4× zoom] indicating the area of G [40× zoom]). H–L, The microscopic findings of the third autopsy patient. H (4× zoom), A thrombus layer on the struts with encapsulated foreign material (augmented in I [40× zoom]). J, A myocardial sample (4× zoom) of this patient in the territory of the stented coronary artery. K and L (40× zoom; black boxes in J), Both show distally embolized foreign bodies. M (4× zoom) and N (40× zoom), Intravascular foreign material in the myocardium of the 73-year-old male patient (fourth patient) mentioned in the text.]}
samples showed thrombus around the stent struts with an amorphous foreign material embedded within this thrombus (Figure 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 (Figure 1J–1L).

Case 4 was a 73-year-old male patient with a history of coronary artery bypass graft surgery 20 years earlier and 9 PCIs (of which the last PCI was 10 year before his death). Furthermore, he underwent transcatheter aortic valve implantation 10 days before his death. The patient died because of sepsis, which was most likely caused by an acute necrotizing cholecystitis. Microscopy images of myocardial samples showed intravascular amorphous, nonrefractile, and nonpolarizable material (Figure 1M and 1N).

**Hydrophilic-Coating Material in Thrombus Aspiration Specimen**

Thrombectomy samples from 205 patients with PCI 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 3 most frequently used guidewires, foreign material was most often observed in cases in which the HT Whisper was used (71% of the thrombus sections 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 3 groups were statistically significant (P value with χ² test: 0.040; Figure 2). The percentage of observed foreign material in the group with unknown guidewire (47%) was comparable with the whole group (45%).

![P-value for trend: 0.040](image)

**Figure 2.** Differences in the frequency of foreign material in thrombus specimen found between the 3 most used coronary guidewires. BMW indicates balance middle weight; and HT, high torque.
Histopathologic Conformation of the Source of the Hydrophilic Coating

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

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Figure 3. Histopathologic appearance of hydrophilic-guidewire coating. A–F, left, Examples of foreign material found in thrombus specimen obtained from coronary thrombus aspiration. G–L, right, Polymer (Pm) with hydrophilic coating from a balance middle weight (BMW) guidewire embedded in placental specimen. Note the similarity between the foreign materials found in the thrombus specimen and the hydrophilic coating on the polymer guidewire cover (black arrows).

Discussion

The most important findings of this study are (1) hydrophilic coating materials were found in almost half of the coronary thrombus specimen examined, suggesting the detachment of coatings from guidewires during thrombus aspiration; (2) the frequency of occurrence of these coating detachments was different between the different guidewires used; (3) material were found in 10% of deceased patients undergoing autopsy who had a past medical history of PCI, in 1 patient, 10 years after the last PCI procedure; (4) we have confirmed the hypothesis that the foreign material detaches from coronary guidewires by comparing the in vivo histopathologic appearance with the histopathologic appearance of guidewire 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.
Chapter 3

Previous Reports
To our knowledge, distal embolization of foreign material in the myocardium after PCI has only been reported in 5 previous case reports. The first report we found described a 77-year-old female patient who experienced an acute myocardial infarction for which she underwent PCI with stent placement in the right coronary artery and the RCx artery. Two weeks later she had a fatal arrhythmia. Autopsy revealed multiple basophilic, amorphous, focally lamellated, focally granular material in the microvasulature 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 nonrefractile, nonpolarizable foreign bodies were thought to be derived from the hydrophilic coating of the guidewires used. In the 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 histopathologic appearance of the guidewire used and concluded that the hydrophilic coating of this material must have been the source of these embolizations. The fourth report described a case of a 58-year-old male patient who died during PCI of the right coronary artery and RCx because of fatal arrhythmia caused by an evolving myocardial infarction. On autopsy, cylindrical, coiled, basophilic material was seen in the myocardium of the anterolateral wall. The last report we found described a 65-year-old male patient who died 1 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 RCx artery. This foreign material could not be identified in other areas of the heart.

There is also 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 histopathologic examination of biopsies and autopsies. 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 extremity 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 neurointerventional procedures using an infusion microcatheter, autopsy sections revealed intravascular foreign substances suggesting to be derived from the coating of the microcatheters. 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.
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 evaluating the occurrence of distal embolization of hydrophilic coating in a more systematic manner have been lacking.

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 because it is often described as nonrefractile 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%. Because of the retrospective evaluation of the myocardial samples, using 3 randomly selected samples from the myocardial territory of each coronary artery during routine autopsy, we think that the true incidence of distal embolization after PCI is likely >10%. Indeed, we found detachment of hydrophilic coating in 45% of the cases during thrombus aspiration, which is at least suggestive for a >10% incidence of distal embolization 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 Guidewire Types
We have compared how often foreign material was observed in thrombus specimen between the 3 most commonly used guidewires (Figure 4). The differences observed might be explained by the extent of polymer coverage. Figure 4 shows schematic drawings of the used guidewires 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 and hydrophilic coating in purple). We demonstrated that the guidewire which is completely polymer covered (ie, the HT Whisper) was associated with the most frequent retrieval of foreign material in the thrombus specimen, whereas the guidewire without any polymer coverage (ie, HT floppy) has 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 guidewire 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 guidewires, both in patients with stable angina and
in patients undergoing primary PCI for ST-segment–elevation myocardial infarction, remain to be elucidated. The fact that 1 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, 1 might speculate on the other hand that occlusion of small intramyocardial arteries by foreign bodies will lead to impaired cardiac function because of microinfarctions. Chronic inflammation with the presence of eosinophilic granulocytes as a reaction on the foreign material might further attribute to the myocardial impairment.\textsuperscript{5,9} Although distal embolization during PCI is usually clinically attributed to atheroemboli or thromboemboli 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 because 2 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 guidewires used during the procedure. As a consequence, in general, data on guidewire type used are lacking which can be used to investigate the relationship between different guidewires and clinical outcomes. Therefore, we think guidewire type should be captured in the datasets of future clinical trials.

**Limitations**

A first limitation is that we did not prospectively collect the guidewires used during thrombus aspiration. Therefore, we are not completely certain whether the first mentioned guidewire in the PCI report was indeed used for the thrombus aspiration. Furthermore, from the 205 evaluated thrombus specimens, type of guidewire used was unknown in 17% of the cases. However, as mentioned before, most clinical databases used for contemporary clinical trials do not include guidewire 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 guidewire types are needed to investigate whether 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 guidewire type as a variable in their data set to explore whether embolization associated with certain guidewire types have clinical effect. This information is necessary to evaluate whether the benefits of hydrophilic coatings in terms of guidewire passage and trackability outweigh the potential harm done by the distal embolization of detached coating material.
REFERENCES