Incidence of associated events during the performance of invasive procedures in healthy human volunteers

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Highstead, R. Grant, Kevin D. Tipton, Daniel L. Creson, Robert R. Wolfe, and Arny A. Ferrando. Incidence of associated events during the performance of invasive procedures in healthy human volunteers. J Appl Physiol 98: 1202–1206, 2005. First published November 24, 2004; doi:10.1152/japplphysiol.01076.2004.—Metabolic investigations often utilize arteriovenous sampling and muscle biopsy. These investigations represent some risk to the subject. We examined 369 studies performed in the General Clinical Research Center between January 1994 and May 2003 for events related to femoral catheterization and muscle biopsies. Incidents were further examined by age (younger: 18–59 yr, n = 133; and older: 60–76 yr, n = 28). There were no clinically defined major complications associated with either procedure. The incidence of femoral catheter repositioning or reinsertion was higher in the older group (25.5 vs. 9.7%). There was no difference in the incidence of premature removal of catheters, ecchymosis or hematoma, or the persistence of pain after discharge. The occurrence of all incidents did not increase with multiple catheterizations. Muscle biopsy was associated with infrequent ecchymosis or hematoma in both groups (1.1 and 3.6% in younger and older groups, respectively). Both procedures entail a small likelihood of a vagalike response (3.3% overall), resulting in nausea, dizziness, and rarely a loss of consciousness. These results indicate that, in skilled hands and a defined clinical setting, the incidents associated with femoral catheterization and muscle biopsy in healthy volunteers are reasonable and largely controllable.

RECENT INVESTIGATIONS INVOLVING the study of human muscle have advanced our understanding of metabolic regulation. The use of invasive clinical procedures is often inherent in these investigations. For example, the study of muscle amino acid, glucose, or fatty acid substrates entails the sampling of blood that delivers substrates to the tissue and blood that drains the tissues. Furthermore, to understand what transpires in skeletal muscle, a sample of this tissue may also be required. For these reasons, many of our metabolic studies entail the cannulation of both the femoral artery and vein, as well as biopsy of skeletal muscle. The code of research ethics dictates that the risk-to-benefit ratio must be such that the greater good to society is outweighed by the minimal risks to human (in this case, normal) subjects. For this reason, it is prudent to review the risk of performing invasive procedures on normal, healthy volunteers.

Previous studies have examined the outcomes of intervensional femoral catheterization in patient populations (5, 6, 11) and the management of volunteers undergoing femoral catheterization (18). However, there is limited information on the risks of femoral catheterization in healthy volunteers, and there have been no reports on the effects of repetitive muscle biopsies in these subjects. Thus we performed a retrospective examination of our metabolic studies to evaluate the effects and associated incidents of muscle biopsies and femoral arteriovenous catheterizations in healthy volunteers.

MATERIALS AND METHODS

Patient population. We reviewed medical records of volunteers who participated in our metabolic research studies between January 1994 and May 2003. This included 161 healthy volunteers, free of clinically detectable disease (116 men, 45 women, 133 between the ages of 18 and 59 yr, 28 between the ages of 60 and 76 yr) who participated in 369 research studies. All studies entailed the use of stable-isotope methodology to determine various aspects of muscle metabolism. Many of our research protocols entail pre- and postinterventional studies, and thus they require the subject to undergo multiple metabolic studies. Volunteers reported to the General Clinical Research Center (GCRC) at The University of Texas Medical Branch (UTMB), Galveston. Volunteers were briefed on all aspects and risks of the study, and they were asked to read and sign a subject consent form. After agreeing to participate, volunteers were screened by medical history, physical examination, and appropriate laboratory analyses to determine adherence to inclusion criteria specific to each study. Volunteers were scheduled for a metabolic study only after review and approval by the protocol physician. All procedures were performed in a clinical setting at the GCRC under the supervision of the protocol physician. All protocols were approved by the UTMB Institutional Review Board (IRB) and the GCRC Advisory Committee. Before the actual metabolic study, volunteers were again thoroughly briefed on procedures and risks, and they were informed that they could withdraw from the study without consequence at any time and for any reason.

Invasive procedures. Our investigations entailed 346 femoral arteriovenous catheterizations and 1,301 muscle biopsies. Femoral catheters were inserted by a physician and secured with sutures to ensure viability throughout the research protocols, many of which included the performance of resistance or treadmill exercise. Both the femoral artery and vein were catheterized on each occasion, and patency was maintained with heparinized saline for 5–10 h for study purposes. Catheters were primarily 3-F or 4-F, 8-cm polyethylene catheters (Cook, Bloomington, IN), and they were inserted under local anesthetic (1% lidocaine) and aseptic technique. Catheters were inserted by experienced faculty physicians from either the Department of Surgery or Anesthesiology. Catheter insertion methodology was consistent and standardized among physicians by use of the Seldinger technique. Vessels were identified with the assistance of anatomic landmarks; femoral pulse; and, after vessel piercing, pressure and color of blood in the insertion syringe or the intravenous tubing. At study completion, sutures were removed and syringes placed on each catheter hub. Catheters were removed separately to minimize the
possibility of arteriovenous fistula. Blood was first withdrawn from the venous catheter to confirm venous blood and absence of clots, the catheter was withdrawn, and pressure was held for 5 min. Blood was then withdrawn from the arterial catheter to confirm the absence of clots, the catheter withdrawn, and hemostasis obtained by direct pressure for at least 10 min. During this time, subjects were observed for active bleeding or the formation of hematoma. The subject was then instructed to remain still in bed for at least 2 h and refrain from Valsalva-type maneuvers. Before discharge from the GCRC, the absence of bruit was confirmed by auscultation of femoral pulse, and vascular sufficiency was confirmed by distal pulse. The absence of fistula was confirmed by vascular sufficiency in the leg and the absence of systemic alterations (i.e., increase in heart rate). Subjects were instructed to avoid strenuous exercise or activity for 24 – 48 h. They were also told to check their femoral region for signs of bruising, swelling, or pain and to contact our staff if any problems arose.

As permitted by Texas state law, muscle biopsies were performed by trained and credentialed PhD-level investigators and/or nurses under the supervision of faculty physicians. These individuals were trained by prescribed program and demonstrated repeated competency to the training physician. After competency was ascertained, approval was obtained by the UTMB IRB and credentialing through the GCRC and Hospital Credentialing Committee. All biopsies were performed under the direction of the faculty or protocol physician. Biopsies were taken from the lateral portion of the vastus lateralis muscle (n = 1,288) or soleus muscle (n = 13) using strict sterile procedures.

Before the muscle biopsies were taken, the skin was cleaned and made sterile with Betadine. A sample of the muscle was removed with the needle 5-mm Bergström needle was advanced into the muscle, and suction was applied. A sample of the muscle was removed with the needle (~50 – 100 mg), and the skin was closed with a suture. To minimize risk of infection and bruising, an antibiotic ointment and pressure dressing were applied. Four hundred milligrams of ibuprofen was given to minimize inflammation, and ice was applied at the end of each study.

Outcomes studied. During each metabolic study, the research and clinical staff noted complications in patient charts during the studies and over a 2-h observation period at the conclusion of each study. Subjects were discharged with verbal and written instructions to call the responsible physician or principal investigator should study-related problems arise. Complications occurring beyond the 2-h observation period required patient self-reporting and subsequent evaluation by UTMB physicians.

Subject charts were reviewed to determine the incidence of post-procedure complications. We initially classified complications of femoral cannulation as outlined in Table 1; %Incidence, percent incidence of events in Table 1. Incidences experienced in a medical intensive care unit setting included the following: vascular insufficiency (thrombosis or loss of distal pulse, pseudoaneurysm, arteriovenous fistula, spasms); bleeding (hematoma, oozing); and infection (abscess insertion site, bacteremia, sepsis). Because our volunteers were discharged from the GCRC after each metabolic study, we also sought to determine the postdischarge effects of femoral cannulation.

Muscle biopsies are not routinely performed in the course of clinical care; therefore, incidents or complications arising from their performance are not readily available. However, based on the nature of the procedure, we determined the incidence of pain, numbness, infection, and bleeding. In addition, we sought to quantify the post-study incidence of these complications. Incidents and events are delineated by aggregate subject population and by two arbitrarily chosen subpopulations (subjects between 18 and 59 yr of age and those between 60 and 76 yr of age).

Statistics. A comparison of percent incidence of each event was made between younger (18 – 59 yr) and older (60 – 76 yr) subjects by using the $\chi^2$ test modified with the Yates correction factor.

RESULTS

Table 1 outlines the incidence and type of events related to femoral line insertion. There were no incidences of major complications such as thrombosis, loss of pulse, fistula, or pseudoaneurysm with femoral catheters. Femoral catheters had to be repositioned or rethreaded at least once in 41 separate incidences (11.8% of total) due to difficulty in blood draw or due to displacement during exercise. Although there were more incidents in the younger group, the event as a percentage of total procedures is statistically higher ($P = 0.004$) in those subjects over 60 yr. Catheters were removed and studies discontinued six times (1.7%) due to loss of patency, four times in the younger group and twice in the older group. Ecchymosis or hematomas immediately after studies were reported in 26 instances (7.5%), and 3 (0.8%) of those instances included bleeding or oozing from the line site. In these cases, pressure was reapplied until hemostasis was achieved, and no further complication was noted. There were no differences between the younger and older groups in the occurrence of ecchymosis after femoral line insertion. Pain at the insertion site was not a frequent occurrence, and only 3 (0.8%) of those instances included bleeding or oozing from the line site.

Table 2. Occurrence of incidents associated with multiple vessel catheterizations

<table>
<thead>
<tr>
<th>Catheterizations/Vessel</th>
<th>Total Catheterizations</th>
<th>No. of Incidents</th>
<th>%Incidence</th>
</tr>
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<tbody>
<tr>
<td>1 ($n = 158$)</td>
<td>158</td>
<td>49</td>
<td>20.9</td>
</tr>
<tr>
<td>2 ($n = 51$)</td>
<td>102</td>
<td>14</td>
<td>18.2</td>
</tr>
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<td>3 ($n = 20$)</td>
<td>60</td>
<td>6</td>
<td>23.1</td>
</tr>
<tr>
<td>4 ($n = 4$)</td>
<td>16</td>
<td>1</td>
<td>16.7</td>
</tr>
<tr>
<td>5 ($n = 2$)</td>
<td>10</td>
<td>0</td>
<td>0.0</td>
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Catheterizations/Vessel, no. of catheterizations per vessel and no. of times this occurred (i.e., 158 vessels were catheterized once and only once; 51 vessels were catheterized once and then a second time, etc.); Total Catheterizations, total aggregate catheterizations performed; No. of Incidents, no. of incidents outlined in Table 1; %Incidence, percent incidence of events in Table 1.
reported in 11 (3.2%) instances, and pain lasting longer than 3 days poststudy was reported in a further subset of 4 (1.2%). The longest duration of reported pain after the end of a study was 8 days. Follow-up ultrasound investigations showed no evidence of deep venous thromboses or diminished blood flow in this volunteer. There were no incidences of infection observed in any of these studies.

Closer examination of the data reveals that the incidence of related events is unchanged with multiple catheterizations per vessel. When the data set was further apportioned to examine the effects of multiple entries or catheterizations within the same vessel, there was 235 occasions where a vessel was catheterized once, 77 occasions a vessel was catheterized for a second time, 26 occasions a vessel was catheterized for the third time, 6 occasions a vessel was catheterized for the fourth time, and 2 occasions a vessel was catheterized for the fifth time. The time between consecutive catheterizations varied according to the study protocol and ranged from 5 days to 6 mo. Table 2 depicts the incidence of any event described in Table 1. These data indicate that the incidence of related events is no greater with subsequent catheterizations within a given vessel. In other words, the possible occurrence of a related event is just as great with the first study or catheterization as it is for subsequent entries. Despite these findings, we have since limited the number of catheterizations for each subject to four per vessel.

Table 3 outlines the incidence and type of events related to muscle biopsies. A total of 1,301 muscle biopsies were obtained during 362 metabolic studies. Most studies entailed multiple biopsies from one or more incision sites. The most common occurrence was ecchymosis or hematoma, reported in 18 (1.4%) instances, while bleeding or oozing was reported in 2 (0.2%) instances. Although the incidence of ecchymosis or hematoma entailed a small percentage of each age group, it was statistically greater in the older group ($P = 0.025$). There were no occurrences of infections. There was also no report of abnormal or unacceptable scarring, most likely attributable to the proper use and removal of sutures. Pain and/or redness around the biopsy site lasting >3 days were reported on 4 (0.3%) occasions. This response generally lasted less than <2 days, but one volunteer reported continued biopsy site hyperesthesia 4 mo poststudy. One subject in the 18- to 59-yr group lost peripheral superficial sensation on a 4-in.-diameter spot near the biopsy site. This was later diagnosed as a neuroma by the faculty physician, and the patient was followed for several months. A final outcome is not available, however, because the subject did not continue with follow-up.

On careful review of the records, these metabolic studies and accompanying procedures entail a small risk of other adverse responses. Table 4 outlines these responses that include light-headedness (including vertigo and tinnitus) or a loss of consciousness. These events occurred in a total of 12 studies (3.3%). Exercise alone produces these symptoms when performed at a sufficient intensity or in untrained subjects (9, or 2.4%). A vagal response that resulted in loss of consciousness occurred on three occasions (0.8%). This response could be associated with intravenous catheter insertion, peripheral or femoral, or with muscle biopsy. When the incidents described in Table 4 occurred, subjects were immediately evaluated by a physician and, if appropriate, given the option to terminate the study or continue. The metabolic study was discontinued, however, on only one (0.002%) occasion. The data from those studies that were continued were carefully examined for evidence of outlying values. Furthermore, there were no differences between age groups in the occurrence of these incidents.

**DISCUSSION**

The careful evaluation of over 369 metabolic studies in healthy volunteers reveals that major complications are unlikely when studies are performed by a skilled research team. In the placement of 346 femoral artery and venous catheters, complications such as infection, vascular insufficiency, pseudoaneurysm, or arteriovenous fistula that may be seen in intensive care unit settings were not experienced. Our data indicate that the predominant incidents associated with femoral catheterization and muscle biopsies represent reasonable and manageable risks when performed in the clinical GCRC setting. Although the incidence of these events is fairly low, some may be more prevalent in older volunteers.

The importance of arteriovenous sampling and muscle biopsies to metabolic research cannot be underestimated. Because most of our studies focus on the investigation of muscle metabolism, the ability to sample inflow (femoral artery), outflow (femoral vein), and the tissue itself (biopsy) enables the determination of substrate kinetics in and across skeletal muscle. This methodology has allowed us to determine the effects of specific nutrients (4, 20, 25–27), hormonal influences

<table>
<thead>
<tr>
<th>Table 4. Other incidents requiring attention</th>
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<tr>
<td><strong>Studies (Total $n = 369$)</strong></td>
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<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Nausea, dizziness, or light-headedness</td>
</tr>
<tr>
<td>Nausea, dizziness, or light-headedness after exercise</td>
</tr>
<tr>
<td>Loss of consciousness or vagal response</td>
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(2, 9, 10), exercise (3, 23, 24), and other physiological alterations (7, 8) on muscle metabolism. The arteriovenous balance and muscle biopsy techniques have been widely used by others as well (1, 12–17, 19). These techniques enabled the advancement of our understanding of the metabolic mechanisms and substrate regulation throughout a wide range of physiological conditions. Furthermore, quantification of the “normal” response to nutritional or hormonal signals is inherent in the interpretation of clinical alterations.

An examination of the events associated with these metabolic studies reveals two types of events related to research volunteers: those that can be reasonably controlled by the investigative team, and those that are out of clinical control but require treatment. The former are those outlined in Tables 1, 2, and 3, whereas the latter are represented by those events in Table 4. The incidents described in Tables 1–3 are minimized in the hands of skilled “technicians” and with proper nursing and clinical controls. With standardization of methodology and the adherence to performance standards, technician variability and incident occurrence are minimized. For example, the performance of a muscle biopsy is standardized by one or two physicians who train, observe, and supervise a number of successful iterations before credentialing. The adherence to these defined procedures minimizes risk, subject discomfort, and related incidents.

With femoral catheterization, the incidence of related events does not increase with subsequent vessel entries/catheterizations (Table 2). Although these incidents are minimized to a reasonable degree, they cannot be alleviated entirely and will always require continued investigator and clinical vigilance. If there is a potential pitfall in the data described in Tables 1 and 2, it could be in the incidence of persistent symptoms. Although our nursing staff is diligent about poststudy and discharge follow-up, these data are subject to underreporting due to the inability to locate or speak to the subject or to the subject’s hesitancy to report any problems. Thus the estimation of longevity of events depends a great deal on subject self-reporting and has the potential to be underestimated. However, it is unlikely that a large percentage of these events are persistent, because the magnitude of the incidence was minor when documented during study. Furthermore, IRB regulations stipulate that serious and unanticipated adverse events be reported within 24 h. Thus the presence of such events would be, and is, well documented.

Table 4 lists “other incidents requiring attention,” which could be considered uncontrollable events. Although the incidence of these events is low, they nevertheless pose risk to the subject and jeopardize successful completion of the research protocol. These risks are routinely described in the subject consent forms to alert the subject to additional risks outside of those directly related to study procedures. Although it is impossible to forecast individual susceptibility to a vagal response, it is prudent to have a well-rehearsed plan in place to minimize further subject risk. In our experience, there is little or no relationship between the degree of invasiveness and the likelihood of vagal response. The events outlined in Table 4 are as likely to occur with insertion of a peripheral catheter or a butterfly blood draw, or with a muscle biopsy or femoral line. When such a response occurs, the subject is placed in a head-down (Trendelenberg) bed position, fluids (intravenously or by bolus) are administered, and blood pressure is closely monitored. The study physician is immediately alerted and examines the subject. If clinically sound, the subject is given the option of continuing with the protocol. Of the 24 total incidents, only 1 subject chose not to continue with the study. It is prudent, however, to exclude such subjects from future studies requiring invasive procedures.

The observed difference between subject groups in percent occurrence of femoral line repositioning and reinsetion and biopsy-related ecchymosis is not unexpected. Older individuals have a higher degree of vessel plaque and a reduced vessel compliance that would impede cannulation. Although it is tempting to speculate that the biopsy-related ecchymosis could be related to the daily use of aspirin that is commonly prescribed for older individuals, studies indicate that the defect in primary hemostasis largely disappears 48 h after the last dose (22). Although the patients were asked to abstain from aspirin at least 1 wk before the metabolic study, it has been shown that the concomitant use of other drugs may affect systemic hemostasis in older people (21).

Finally, it should be mentioned that there were no problems associated with the infusion of stable isotopes or the frequent sampling of blood from indwelling catheters. The use of isotope material that is sterile and pyrogen free, strict attention to the preparation of these compounds, and proper clinical procedures for catheter blood draws prevented the occurrence of any related problems.

In summary, this retrospective examination of metabolic studies indicates that, in skilled hands and with appropriate clinical control, femoral catheterization and muscle biopsy procedures represent a relatively minor and reasonable risk in healthy volunteers. The risks, however, are not zero and must be continuously mitigated with heightened vigilance of the investigators and clinical personnel. When judged in light of the risk-to-benefit ratio, the potential benefits of scientific outcomes outweigh the existing risks. Furthermore, the accompanying risks can be successfully managed to ensure no lasting complications or problems.

GRANTS

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