General Anesthesia for Whole-Body Hyperthermia

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Abstract

General anesthesia was used to facilitate 259 whole-body hyperthermia treatments in 90 patients. These patients fell into American Society of Anesthesiologists Classifications 3 (moderate to severe systemic disease) and 4 (severe systemic disease with life-threatening potential). Whole-body hyperthermia imposes severe stress on cardiopulmonary and renal function. In this series, elevation of temperature from 38° to 41.5° raised cardiac output to approximately 200% of control, while oxygen consumption rose 35%. General anesthesia provides conditions which allow for more precise control and support of vital signs, fluid requirements, and blood gases.

Introduction

We have been using general anesthesia in WBH treatment of cancer for 3 years. Ninety patients have received general anesthesia for 259 treatments. This discussion will present the background considerations for the development of our anesthetic techniques, some of our experience, and our evolving impressions relating to unresolved problems and possible avenues of future investigation.

Discussion

Reasons for General Anesthesia

During WBH with or without chemotherapy, anesthesia is an integral part of the therapy rather than an undesirable but necessary adjunct. Specific control over blood pH, P_{O_2}, P_{CO_2}, and organ blood flow is essential to the successful hyperthermic treatment and is distinctly different from the anesthetic management of routine surgery.

There is compelling physiological and therapeutic impetus for using general anesthesia, in addition to helping the patient tolerate the discomfort of the rapid heating process and the attendant high body temperatures. The physiological stress of sustained core temperatures in excess of 41.5° is such that both extensive invasive monitoring and numerous pharmacological interventions are necessary. Both of these needs are best managed in the controlled environment provided by general anesthesia.

Physiology of Heat Stress

Heat stress places extreme demands on the circulatory system and sweating functions, as well as water and electrolyte balance, renal function, and neurosystem control (9, 13-16, 20, 21, 24). The anesthesiologist can support, modify, or interrupt some of these systemic responses.

The responses to heat stress per se are described extensively (13, 14). Sweating is the most conspicuous response associated with the rise in body temperature. The approximate maximum sweating rate is 10 to 12 ml/min, which is reached when core temperature has risen approximately 1° (13). If one assumes a starting value of 38°, attainment of 42° in approximately 2 hr, and maintenance of 42° for an additional 2 hr, then the volume of fluid loss could be more than 5 liters over the course of the treatment and recovery period. These calculations, with reports of sweat fatigue, may not apply at such extreme temperatures at 42°.

In nonacclimatized humans, the sodium content of sweat can be 40 to 50 milliequivalents/liter. Under extreme conditions that cause very high skin temperatures, the osmolarity of sweat can approach that of plasma. Potassium concentration is approximately 10% of sodium concentration whether the patient is acclimatized or not. Additional water may be lost by sublimation or in respiratory gases, urine, and feces.

In conscious humans, hyperventilation occurs in response to increased temperature beyond the effects of increased CO_{2} production, causing P_{CO_2}, corrected to 37°, to fall below normal, perhaps implicating a direct effect of heat per se on respiration (13). In the anesthetized, paralyzed, WBH patient, ventilation is therefore controlled for therapeutic purposes.

The depressant effect of heat on water diuresis is well known (13). Heat exposure that elicits a sweating response may depress urine flow markedly. This suggests that the physiological response is the initiation of water retention, which is not, initially at least, dependent on antidiuretic hormone (13). The pronounced effect on urine flow may be explained in part by the substantial influence of heat on renal hemodynamics (13). Exposure to heat depresses renal blood flow and may depress glomerular filtration. Heat alone, however, does not reduce urine output below a minimum obligatory volume.

The hemodynamic effects of hyperthermia have been described by Kim et al. (12), who observed patients’ responses to increasing temperature. The most remarkable changes in hemodynamics were in heart rate, which increased 50%, and in cardiac index, which increased 70%, both at 41.5°, as compared to basal conditions. Mean arterial pressure fell approximately 15%. Central venous and pulmonary capillary wedge pressures fell approximately 50 and 45%, respectively. These changes occurred with a 350% increase in circulating norepinephrine and a 55% increase in epinephrine levels.

Much of the cardiovascular response to hyperthermia can be interpreted as an effort to transfer heat from the core to the surface where it can be more effectively dissipated by the mechanisms of radiation, conduction, convection, and evaporation. The profound vasodilation and vasoconstriction involved in heat stress causes changes in the distribution of blood flow to various organs. Additionally, the effects of anesthetic drugs can alter organ perfusion.

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2 The abbreviations used are: WBH, whole-body hyperthermia; ECG, electrocardiogram; PCWP, pulmonary capillary wedge pressure.
Pretreatment Anesthetic Evaluation

Functional and Drug History. The American Society of Anesthesiologists classification of patients with regard to physical status is: Class 1, healthy, normal patients without a systemic disease process; Class 2, patients with only mild systemic disease or ramifications thereof or patients receiving only modest drug therapy; Class 3, patients with moderate-to-severe systemic disturbances (e.g., angina pectoris, pulmonary insufficiency, or advanced hepatic disease); Class 4, patients with severe systemic disturbances that continually threaten life (e.g., cardiac insufficiency or pulmonary dysfunction of massive infiltrates); Class 5, moribund patients.

Our patients presenting for WBH are usually in Class 3 or 4. They have generally been receiving other cancer therapy with remarkably severe side effects. For example, many WBH patients have received radiation doses that have caused serious reductions in pulmonary reserve. Furthermore, the nature of metastatic disease and the effects of therapy are such that, often, little can be done to improve the patient’s condition before WBH treatment. However, knowing what to expect and anticipating problems are essential in managing these cases. We therefore have a weekly conference for the anesthesiologists, oncologists, and support personnel involved in the WBH therapy in order to discuss, in detail, future and past cases. Salient features are emphasized, and additional evaluation is obtained when appropriate.

In addition to the anesthesiologist’s usual concerns for drug therapy, it is necessary to anticipate the presence of unique agents in the patient with metastatic cancer. For example, the cardiotoxic effects of doxorubicin hydrochloride (Adriamycin) may not be obvious in the unstressed patient, but a reduced myocardial reserve may become evident during anesthesia, particularly with the added stress of WBH (4). The problem can become particularly difficult, since these patients may be unresponsive to the usual therapies. For example, one report describes a dramatic interaction of an anticancer drug, cyclophosphamide, with a potent inhalation drug, halothane (25). Data suggest that exposure to 0.5% halothane for 2 hr, a very modest dose, dangerously increases the toxicity of cyclophosphamide.

Cancer patients who are candidates for WBH frequently are taking mood-altering drugs. Monoamine oxidase inhibitors form stable complexes with monoamine oxidase, and catecholamine concentrations in nerve terminals increase. Consequently, sympathetic activation during anesthesia may precipitate severe hypertensive states. Also, monoamine oxidase inhibitors and analgesics can interact, thus causing hypertensive crises, severe hypotension, tachycardia, convulsions, or respiratory arrest (22). Tricyclic antidepressants are another class of troublesome drugs. Their presence during the use of halothane has been implicated in unanticipated fatal arrhythmias.

Cardiac, Pulmonary, and Renal Problems. Due to the nature of the patient’s disease and the usual medical care, the WBH candidate has generally been carefully evaluated, treated, and monitored for pathology in addition to the metastatic cancer. Anesthesiologists generally focus on aspects of disease or treatment that are potential intra- or immediate posttreatment problems. Congestive heart failure and angina are difficult problems for WBH patients, since our concern is to maintain a sufficient circulating volume, thereby sustaining renal function. However, fluid overload would compromise an already diseased heart or promote pulmonary interstitial accumulation of fluid. WBH candidates frequently have elevated creatinine levels, indicating impaired renal function that may further be aggravated by hyperthermia per se and which may alter anesthetic drug elimination.

Brain Metastases. Our group does not submit patients with known brain metastases to WBH. Preoperative evaluation includes a computer-assisted tomography scan of the head to find evidence of metastatic disease. We believe that the risk of tumor hemorrhage, infarct, or massive edema from rapid tumor necrosis is too great to justify such investigative therapy.

Gated Cardiac Nuclear Scan. We use the gated cardiac nuclear scan with exercise stress to provide an indication of cardiac reserve and the patient’s probable ability to withstand the stress of WBH. The test suggests the probability of a patient developing myocardial ischemia, failure, or dysrhythmias during treatment. However, the exercise stress may not be sufficient to fully predict whether the patient has sufficient cardiac reserve to withstand WBH treatment.

General Anesthesia Issues

Because of the nature of WBH therapy, patients are seldom considered as candidates until late in the course of their disease when the prognosis is usually grim. From the anesthesiologist’s point of view, this situation is very different from the usual surgical situation in which cases are either elective or emergent. Elective surgery is frequently postponed if there are correctable problems that would reduce the risks of anesthesia. With some candidates for WBH, prolonged delays to improve concomitant problems would further reduce the chances for success of the WBH treatment. Other patients have problems that simply cannot be improved in the time available. For these reasons, we frequently undertake more difficult and complex problems than we would for elective surgery. The risks, however, are discussed with the patients in considerable detail beforehand.

Monitoring. We continuously monitor ECG, direct arterial pressure, and pulmonary artery pressures. Direct arterial monitoring, in addition to providing accurate continuous blood pressures, facilitates frequent blood gas sampling. We interpret blood gases at patient temperature rather than at 37°C, the measurement temperature. Our experience indicates better correlation be-
tween patient temperature arterial blood gases and patient responses such as ECG changes and respiratory efforts. An integral part of the WBH therapy is control over tissue gas tensions and acid-base status. Blood gases guide the therapeutic decisions. Ventilation is adjusted to permit $P_{a}CO_{2}$ in the 35 to 40 torr range, since we aim for a mild acidosis relative to the $pK_{a}$ of water at the patient’s temperature. Inspired oxygen concentration is adjusted to maintain $P_{a}O_{2}$s in the range of 70 to 90 torr to promote tumor hypoxia and enhance the cytotoxicity when WBH is combined with chemotherapy. This frequently results in $F_{O_{2}}$s of as low as 0.20. Hypoxic damage to other organ systems is avoided by close monitoring of the ECG and, in particular, mixed venous $O_{2}$ from the pulmonary catheter. We currently consider a mixed venous oxygen tension of 35 torr to be the lowest acceptable value.

Pulmonary artery pressures and PCWP are monitored and continuously guide fluid administration to maintain adequate filling pressures based on: (a) initial PCWP at normal temperature; (b) maintenance of adequate systemic blood pressures, considering the patient’s normal pressure; and (c) maintenance of adequate urine flow.

We believe that urine output most accurately represents the state of visceral organ perfusion. In most stress states, urinary output is depressed; maintenance of urine flow gives reasonable assurance of adequate visceral flow. This indicator of organ flow is lost if diuretics are used to maintain urine output. Rather than use diuretics if urine volume falls below 100 ml/hr, we prefer low doses of dopamine to increase urine volume. If this maneuver is not successful, termination of the treatment is considered.

Nutritous Oxide. We use nitrous oxide as a diluent of oxygen and as a weak analgesic/hypnotic. Nitrous oxide reduces the need for other anesthetics, in particular, the potent inhalational anesthetics. In vitro nitrous oxide has direct myocardial depressant effects, but the effects are substantially fewer than those of the halogenated inhalational agents. However, in vivo, there appears to be only a mild sympathetic stimulation.

Potent Inhalational Agents. Halothane, enflurane, and isoflurane, the major inhalational agents, share many general characteristics. Each is a potent myocardial depressant, an effective vasodilator, and a respiratory depressant. Individual characteristics distinguish the drugs and are the basis for the selection from among them. These agents are discussed extensively in standard texts and recent reviews (2, 5, 9–11).

The hepatotoxicity of halothane is probably due to a metabolite; this metabolism would be expected to increase during hyperthermia. Furthermore, we feel that reduced oxygen tensions would enhance halothane toxicity. Enflurane is more stable than is halothane. However, trace amounts of inorganic fluoride have been detected. The major disadvantage of enflurane is that this agent is the most potent myocardial depressant of the available agents. Isoflurane, chemically the most stable of the agents, is also a myocardial depressant and has the additional disadvantages of frequently causing tachycardia and hypertension.

During WBH, there is little need for such powerful anesthetic agents, since noxious stimulation is considerably less than during surgery. We feel that the disadvantages of these agents clearly outweigh any advantages and, therefore, we no longer use this group of agents during WBH treatments.

Narcotics. Recent discussions point out that narcotics, in general, have little effect on the cardiovascular system (17, 23). For this reason, we use narcotics with nitrous oxide as a basis of our anesthetic technique. Fentanyl and butorphanol are the 2 drugs most frequently selected. Unless a patient is narcotic dependent, butorphanol is used. In patients for whom the antagonist properties of butorphanol are undesirable, we choose fentanyl. The primary advantage of butorphanol is its ceiling effect on respiratory depression, which minimizes posttreatment respiratory problems (11). Fentanyl has a short half-life, seldom causes significant hypotension, and is easily reversed by naloxone; it is therefore our second choice among narcotics (1). Muscle Relaxants. Since there is little in the way of painful stimulation during a WBH treatment, we are able to keep patients unconscious and amnesic with relatively small amounts of narcotics and lorazepam. To ensure that patients do not move and to facilitate control of ventilation, we paralyze all patients with a long-acting muscle relaxant. Muscle relaxants are extensively reviewed in standard texts and monographs (6, 7, 18). Because of the long duration of WBH treatments, the short-acting depolarizing muscle relaxants are inappropriate. Succinylcholine is suitable for induction but, with prolonged use, it produces a mixed or Phase 2 block, which is difficult to manage and which cannot be readily reversed. For continued muscle relaxation after induction, there are 3 drugs from which to choose, d-tubocurarine, pancuronium, and atracurium. d-Tubocurarine is predictable and readily reversed by cholinesterase inhibitors. Disadvantages are histamine release and ganglionic blockade. Both of these properties compound problems in the vasodilated WBH patient. We use pancuronium, since it is predictable and useful for intubation; it can also be continued throughout the case, and it is reliably reversible. Tachycardia is an occasional side effect at higher doses. Atracurium has become available recently. The unique Hoffman elimination is an advantage, since reduced cumulative effects make reversal more rapid and reliable than with other agents. However, our experience with this drug is limited.

Positioning and Effective Heating. Positioning the patient during a WBH treatment is critical for both effective heating and patient care. The combined effects of high temperature, hypermetabolism, reduced $P_{a}O_{2}$, and vasodilation can rapidly lead to localized burns and/or tissue necrosis wherever pressure points occur. Our problems have been greatly reduced since the acquisition of a specially modified (maximum temperature increased to 50°C) Clinitron bed. In this bed, the patient “floats” on a bed of fine silicon particles suspended by forced hot air. The hot air helps to heat the patient, and this “floating” prevents pressure points on the patient’s dorsal surface. To cover the patient’s ventral surface, we use a hot water blanket and apply foam padding over all prominences to avoid pressure points. Over the water blanket, we place a reflective blanket to prevent radiation heat loss (3).

With this technique, we are able to heat patients routinely to 42°C within 2 hr without the dangers and complications of extracorporeal blood warming. However, use of the technique requires considerable care and experience to prevent overheating, since the Clinitron bed has a rather slow response time for temperature changes. Also, anticholinergics must be used to inhibit sweating, since the air forced by the bed can result in rapid cooling due to evaporation of any sweat allowed to form.

Posttreatment Management. One-third to one-half of the patients are extubated in the operating room. Fewer than 10% of the patients require intubation and ventilatory support for...
more than 60 to 90 min. Patients who do require longer duration of intubation and/or mechanical ventilatory support are those who develop significant shunting during the procedure, frequently because of pulmonary tumor involvement. Whether extubated or not, posttreatment regimen requires the lowest safe FiO2 to continue effective treatment during the cooling phase. This is sometimes a problem, since intensive care unit and recovery room nurses are inclined to increase FiO2s and aim for Pao2s in excess of 100 torr, both of which are contrary to the goals of an effective WBH treatment.

Current Experience

Anesthetic Techniques. We use endotracheal general anesthesia as proposed by Henderson and Pettigrew (9) and Pettigrew et al. (20, 21). We believe that the patient is best supported and protected by this method. Muscle relaxants are used to eliminate coughing and movement and to reduce the dosages of other depressant drugs.

Previously, the potent inhalation agent isoflurane was the primary anesthetic agent used. The major difficulties were: (a) tachycardia; (b) hypotension; (c) large fluid volume replacement; (d) requirement for supplemental vasoactive and cardiotonic drugs; and (e) prolonged posttreatment intubation. Because of these problems, we now use nitrous oxide and i.v. drugs, including narcotics, thiopental, an amnesic agent, and a muscle relaxant.

Compared to surgery, there is relatively little discomfort during WBH treatments and, consequently, only mild analgesia is required. The primary objectives are hypnosis and amnesia. Fentanyl and butorphanol are the narcotics we use. Their relative merits and specific indications for use were discussed previously. For the purposes of WBH, the combination of a narcotic and a benzodiazepine seems to be synergistic, providing both more analgesia and more hypnosis/amnesia than either could alone. We use lorazepam most frequently, but occasionally we use diazepam. Lorazepam is given preoperatively, 1 to 2 mg p.o. and, following induction of anesthesia, 1 to 2 mg more may be given i.v. Thiopental is used for induction.

Currently, the relaxant used is pancuronium.

The final factor to consider is the use of nitrous oxide. Although it is a relatively weak anesthetic in itself, it possesses clear ability to supplement other agents. At usual concentrations, it also provides analgesia and is a useful hypnotic agent. By using nitrous oxide as a diluent, we can also control the FiO2, thus ensuring that arterial PO2 does not exceed 100 torr unless we desire otherwise. Presumably, this approach maximizes the lethal effect of heat by minimizing the oxygen supply to the assumed hypermetabolic tumor cells.

Temperature Monitoring. We have been concerned with regional temperature differences—in particular, brain and heart temperatures. To obtain an index of brain temperature, 3 techniques have been compared: nasopharyngeal; tympanic membrane; and retrograde placement of a thermistor into the jugular bulb. These techniques show close agreement and less than 0.2°C difference and are in close agreement with those of the pulmonary artery catheter, esophageal, and rectal temperatures. As a result, we believe that with our WBH technique, the body is nearly uniformly heated.

Fluid Requirements. The fluid requirement necessary to replace sweat losses has been substantial. This requirement has been reduced considerably by using glycopyrrolate to prevent sweating. Fluid loads are administered as described above. Additionally, to minimize the large volumes of crystalloid fluids required to maintain adequate filling pressures and urine output, we have used albumin, either concentrated or in a 5% solution. Usually 50 g are administered at the beginning of the treatment and more is given during the treatment as indicated by the PCWP.

As a general rule, urine output guides the administration of crystalloid, and albumin solutions are given as indicated by the arterial and PCWP pressures. RBC solutions are seldom given unless other measures fail to maintain the mixed venous PO2 at 35 torr or greater. This approach has substantially reduced the incidence of fluid overload and pulmonary edema in our patients.

Cardiovascular and Metabolic Response to WBH. WBH treatment imposes great stress on all of the physiological systems. However, this stress response is most conspicuous as regards the cardiovascular system.

Our measurements suggest that the cardiovascular response is in excess of that required to meet the increased metabolic demands of WBH. Chart 1 demonstrates that mixed venous oxygen tension continues to rise despite increased body temperature, increased oxygen demand, and decreased arterial oxygen tension. Arterial oxygen tension falls during WBH because, in an effort to increase tumor kill, we reduce inspired oxygen to reduce arterial oxygen tension between 65 and 90 torr. Chart 2 provides further evidence of the excess of the cardiovascular response, demonstrating a continuing decrease in the arterial-venous oxygen content difference as temperature increases. Finally, Chart 3 compares the increase in oxygen consumption and cardiac output. Cardiac output appears to increase 3-fold that required to satisfy the increases in oxygen consumption. We interpret the above results as indicating that the excess increase in cardiac output is an abortive attempt to dissipate heat by greatly increasing cutaneous and peripheral blood flow.

Future Investigational Needs

Fluid Requirements. We have been impressed with the degree of effort required to control fluid administration to prevent intrapulmonary shunting. Nevertheless, sufficient fluids must be administered to provide an active, or at least acceptable, diuresis. Insight into this management dilemma could be enhanced by studies of renal function, pulmonary water studies, and the effects of pharmacological maneuvers, such as low-dose dopamine infusion.

Hyperdynamic State. WBH is an extremely stressful mode of therapy to impose on a patient. About 1 candidate in 5 is refused treatment due to failure to improve or maintain adequate cardiac ejection fraction during exercise stress testing. Modification of the cardiovascular response to WBH may make this treatment modality available to a larger number of patients. As is evident in other areas of medicine, the physiological response to extreme conditions is not always the manner best suited to viability. For example, in cardiogenic shock, vasodilators have sometimes proven to be useful. Perhaps short-acting β-blockers will prove to be a valuable adjunct in reducing what appears to be unnecessary tachycardia and increased cardiac output in response to hyperthermia. If visceral flow can be maintained, massive periph-
Oxygen content was calculated from direct measurements of saturation, hemoglobin, and P.O₂ at 37°. Values (mean) obtained from 0.5° above and below were assigned to the indicated temperatures. Bars, S.D.

Chart 1. Mixed venous P.O₂ versus temperature. Values (mean) obtained from 0.5° above and below were assigned to the indicated temperatures. Bars, S.D.

Chart 2. Arterial-venous (A-V) oxygen content differences versus temperature. Oxygen content was calculated from direct measurements of saturation, hemoglobin, and P.O₂ at 37°. Values (mean) obtained from 0.5° above and below were assigned to the indicated temperatures. Bars, S.D.

Chart 3. Cardiac output and oxygen consumption versus temperature. Cardiac output was determined by thermal dilution. Oxygen consumption was calculated using cardiac output and oxygen content. Values (mean) obtained from 0.5° above and below were assigned to the indicated temperatures. Bars, S.D.

General anesthesia for WBH

Other vasodilation might be blunted. If venous P.O₂ from appropriate critical regions could be monitored, perhaps more significant lowering of arterial P.O₂ could be imposed, or patients with reduced cardiac reserve could survive WBH treatments. These and other challenges remain to be carefully studied. We are preparing to gradually initiate modifications of our current regime and to carefully assess the results in hopes of reducing the cardiovascular stress.

Summary

WBH imposes severe cardiovascular and renal stress upon patients. The patients subjected to such therapy often suffer from the physiological stress of the metastatic disease, perhaps with changes associated with previous chemotherapy or radiation. In addition, these patients often fall into the age group which is noted for degenerative changes. Because of these combined problems, we believe that general anesthesia provides the best environment for support of the patient and, in addition, provides conditions which may enhance the effectiveness of hyperthermia.

In order to offer the therapy to a greater number of patients, studies must be undertaken to determine which, if any, physiological responses to heat may be controlled or modified without additional hazard.

References

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