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Review

A Literature Review: The Effects of Magnetic Field Exposure on Blood Flow and Blood Vessels in the Microvasculature

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The effect of magnetic field (MF) exposure on microcirculation and microvasculature is not clear or widely explored. In the limited body of data that exists, there are contradictions as to the effects of MFs on blood perfusion and pressure. Approximately half of the cited studies indicate a vasodilatory effect of MFs; the remaining half indicate that MFs could trigger either vasodilation or vasoconstriction depending on initial vessel tone. Few studies indicate that MFs cause a decrease in perfusion or no effect. There is a further lack of investigation into the cellular effects of MFs on microcirculation and microvasculature. The role of nitric oxide (NO) in mediating microcirculatory MF effects has been minimally explored and results are mixed, with four studies supporting an increase in NO activity, one supporting a biphasic effect, and five indicating no effect. MF effects on angiogenesis are also reported: seven studies supporting an increase and two a decrease. Possible reasons for these contradictions are explored. This review also considers the effects of magnetic resonance imaging (MRI) and anesthetics on microcirculation. Recommendations for future work include studies aimed at the cellular/mechanistic level, studies involving perfusion measurements both during and post-exposure, studies testing the effect of MFs on anesthetics, and investigation into the microcirculatory effects of MRI. Bioelectromagnetics 28:81–98, 2007.

Key words: blood flow; perfusion; blood pressure; nitric oxide; angiogenesis

INTRODUCTION

As our knowledge of human physiology increases and medical diagnosis and treatment becomes more sophisticated, the scale at which research is targeted becomes more minute. In today's society, the need for research involving microstructures within the body and cellular physiology has become increasingly important, as integration of discovery often requires a mechanistic framework. Currently, there is much interest surrounding the microcirculatory system.

Microcirculation is the flow of blood through the microvasculature: the arterioles, capillaries, and venules. It is these vessels that nourish the body's tissues and organs. Two important functions of the microcirculatory system are to alter blood flow according to the varying metabolic requirements of the tissues it serves and to stabilize blood flow and pressure by making local regulatory adjustments [Zweifach, 1977; Neeman and Dafni, 2003; Pittman, 2005; Popel and Johnson, 2005; Segal, 2005; Verdant and De Backer, 2005].

A greater understanding of this vascular network has, and likely will in the future, lead to advances in tissue regeneration, pain control, circulatory disorders, and much more. In fact, several attempts have been

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made to explore the parameters of microcirculation and microvasculature when tissue and/or blood vessels have been exposed to a magnetic field (MF). Recently, MFs have been shown to have positive effects on numerous human systems. For instance, it is documented that MF exposure can provide analgesia, decrease healing time for fractures, increase the speed of nerve regeneration, act as a treatment for depression, and provide other medical benefits [Bassett, 1989; Rubik, 2002; Shupak, 2003; Eccles, 2005; Carpenter, 2006]. Increased knowledge of the influence of MFs on microvascular function may have significant therapeutic potential.

At the moment, there is limited research exploring the potential of magnetism on blood perfusion; however, if an association between MFs and microcirculation is found, there may be a number of clinical benefits. As an example, MF therapy could be useful for the reperfusion of ischemic tissue or during sepsis. When blood flow to a tissue becomes blocked or reduced, necrosis will eventually occur. Local exposure of a MF could potentially result in blood vessel relaxation [Smith et al., 2004] and increased blood flow. Another emerging body of data suggests that MF exposure affects the microcirculation and microvasculature by pushing the system to maintain dynamic equilibrium through biphasic responses [Ohkubo and Okano, 2004]. This type of biphasic effect could trigger a biological system to return to its optimum state. Although there is evidence suggesting that MF exposure has positive applications for circulatory problems, not all studies support this notion. Some researchers have found no effect of MFs on blood flow [Mayrovitz et al., 2001, 2005; Haarala et al., 2003].

Not only do the overall findings within this field of research need clarification, but does the terminology. The terms ''blood flow'' and ''perfusion'' are often used interchangeably within studies and their exact definitions vary. It would appear that the definitions of ''blood flow'' and ''perfusion'' are often characterized as method-dependent definitions. There are many ways of measuring blood flow/perfusion; therefore, the definition of blood flow/perfusion in one experiment might not be the same in another (e.g., the use of radioactive microspheres to measure tissue blood flow in ml/min^2/g [Sinha et al., 2003; Anetzberger et al., 2004], versus a protocol that measures blood flow only in tissues with an active sodium/potassium ATPase pump [Gruwel et al., 1997]). In some research, actual blood flow parameters are considered (e.g., laser Doppler flowmetry), whereas in other research inferences are made based on observed vessel effects (changes in vessel diameter, vessel growth). In this review, ''blood flow'' will be considered as the flow of blood through any vessel, that is, large arteries/veins and microvasculature, and ''perfusion'' will refer to blood flow through the vessels that serve an organ or tissue, that is, the microvasculature. ''Microcirculation'' will therefore be considered as both blood flow and perfusion. ''Microvasculature'' will refer to the microcirculatory blood vessels (arterioles, capillaries, venules) themselves.

This review describes reported effects (and non-effects) of any form of MF on blood vessels and blood flow in the microcirculatory systems of experimental animals and humans. The experiments presented in this review use MFs of varying parameters (varying strengths, static, time-varying, pulsed, etc.). This undertaking was prompted by the emerging body of literature dealing with this topic and the inconsistencies in reported effects. As noted by Cook et al. [2002] in a review on human cognition and electrophysiology, the MF literature is littered with contradictory evidence. We highlight the importance of considering the particular MF parameters that are used in a study, as well as the model tested. It is our aim to provide an overview of all published research in English (up to May 2006, as represented in PubMed (http://www.pubmed.gov) and ISI Web of Knowledge (http://isiwebofknowledge)) involving the effects of MF exposure on microcirculation and microvasculature. Studies addressing MF effects on a cellular level are also included to provide insight into the possible mechanisms of action on the vasculature. This review also considers the use of anesthetics in studies testing the effect of MFs and the MFs used in magnetic resonance imaging (MRI).

LITERATURE REVIEW: MICROCIRCULATION/ MICROVASCULATURE AND MFs

There are numerous processes and chemicals within the microcirculatory system that can be influenced by MF exposure. Most research involving the effect of MFs on microcirculation and microvasculature has focused on static magnetic fields (SMFs); however, the MF parameters that have been used vary between studies, as do other aspects of the experimental designs. Such parameters include field intensity, static versus time changing field, field frequency, pulsed versus non-pulsed field (e.g., duty cycle), localization of exposure, and duration of exposure. When comparing studies, these variables must be kept in mind. The research findings below are organized by modality.

Static Magnetic Fields

The effect of SMF exposure on blood velocity was assessed in a study by Xu et al. [2001]. Peak blood

velocity in the tibialis anterior muscle of mice was measured using a fluorescence epi-illumination system (a fluorescence microscope, charge-coupled device camera, video time generator, tape recorder, and display monitor). It was reported that whole body exposure to a 1 mT SMF for a duration of 10 min led to a 20–45% increase in blood velocity over a period of 45 min post-exposure. No significant increase was noted during the exposure period. When the mice were exposed to a 10 mT SMF, blood velocity was increased by 15% immediately after the initiation of the MF and 45% immediately after the end of exposure. A 0.3 mT SMF did not have any effect. When an electromagnetic field (EMF) (50 Hz) of 1 mT was tested, blood velocity was significantly increased by 27.6% from baseline; whereas when a 0.3 mT (50 Hz) MF was used, no significant change in blood velocity was observed. These results suggest that a 1 mT MF may be the threshold for altering hemodynamics for both SMFs and 50 Hz EMFs. This study clearly demonstrates that various microcirculatory effects are possible depending on the MF parameters used.

Gmitrov et al. [2002] investigated changes in blood flow within the cutaneous tissue of the rabbit ear lobe. A rabbit ear chamber (a transparent acryl-resin chamber) was attached to the ear lobe and then placed under an intravital microscope that allows for the quantification and observation of moving particles. Blood flow measurement by microphotoelectric plethysmography, a simple procedure which provides relative changes in microcirculation in cutaneous tissues based on the light absorption of hemoglobin, occurred pre-, during, and post-exposure. They found that SMF exposure (0.25 T, 40 min exposure) led to a 20–40% increase in microcirculation. Blood flow was significantly increased starting 10 min into the exposure through to 20 min post-exposure compared to sham animals.

In a similar experiment, the effects of a 0.35 T SMF on microcirculation and the arterial baroreflex (reflexes initiated by receptors in the aortic arch that alter peripheral vasomotion) of conscious rabbits were investigated [Gmitrov, 2004]. As was done previously, a rabbit ear chamber was attached to the ear lobe of sedated rabbits and then placed under a microscope. Relative blood flow was assessed non-invasively using microphotoelectric plethysmography. The SMF significantly increased baroreceptor sensitivity, heart rate, mean arterial pressure, and blood flow. Verapamil, a Ca^{2+} channel blocker, decreased the sensitivity of the baroreflex. Vasodilation occurred both after SMF and after verapamil exposure, applied separately. The highlight of their findings was that when the SMF and verapamil were applied simultaneously, the baroreceptor sensitivity and microcirculation were unaffected. This led the author to suggest that the verapamil counteracted the SMF and that the site of action of the SMF on the microcirculation was the Ca^{2+} channels.

Arterial baroreflex was later investigated [Gmitrov, 2005] in sedated rabbits under changing geomagnetic field conditions. Blood pressure and microcirculation were also measured using microphotoelectric plethysmography. A negative correlation was found between geomagnetic disturbance and both microcirculation and baroreflex sensitivity, and a positive correlation was found between microcirculation and baroreflex sensitivity. That is, on days with intense geomagnetic activity, both microcirculation and geomagnetic activity were decreased. This study further suggests that geomagnetic fields directly modify microcirculatory responses rather than general systemic responses. These findings may have serious implications for individuals with ischemic diseases during periods of intense geomagnetic activity.

Using a similar animal model as Gmitrov [2004], Ohkubo and Xu [1997] reported the effects of a 1, 5, and 10 mT SMF. The mean amplitude of microphotoelectric plethysmography was taken to represent vasomotion within the microvasculature. A rabbit ear chamber was attached to the ear lobe of conscious rabbits and then placed under a microscope. Throughout the 10 min exposure period, the SMF induced changes in vasomotion in a non-dose dependent manner. When the initial vessel diameter was less than a certain value, MF exposure caused an increase in vessel diameter (vasodilation). In contrast, when the initial vessel diameter was greater than a certain value, the MF exposure caused a decrease in vessel diameter (vasoconstriction). Based on these results (and more to follow), it would appear that the initial state of the vessel is of importance when considering MF effects on microcirculation and microvasculature.

This idea is reflected in the following studies. Okano et al. [1999] reported biphasic effects (activation/inhibition) of a 1 mT SMF on cutaneous microvasculature of conscious rabbits using microphotoelectric plethysmography and intravital microscopy. When they pharmacologically induced high vascular tone using norepinephrine to cause vasoconstriction, the SMF exposure led to increased vasomotion and caused vasodilation. In contrast, when they induced low vascular tone using acetylcholine to cause vasodilation, the SMF exposure led to decreased vasomotion and caused vasoconstriction.

In a later experiment by Okano and Ohkubo [2001], their previous work on cutaneous microvasculature of conscious rabbits was extended (1 mT SMF,

30 min exposure). This study focused on blood pressure changes associated with SMF exposure. When blood pressure was increased using a nitric oxide synthase (NOS) inhibitor (vasoconstrictor), exposure to a SMF caused a significant decrease in blood pressure during and post-exposure, and led to vasodilation. This led to a significant increase in blood flow, measured using microphotoelectric plethysmography, after 10 min of exposure through to 40 min post-exposure. Alternatively, when blood pressure was decreased using a Ca^{2+} channel blocker (vasodilator), the SMF caused a significant increase in blood pressure during and post-exposure, and led to vasoconstriction. This led to a significant decrease in blood flow for 10 min during exposure.

The ability of a SMF (5.5 mT, 30 min exposure) to alter blood pressure was again tested on conscious rabbits with pharmacologically induced hypertension [Okano and Ohkubo, 2003a]. Norepinephrine or a NOS inhibitor was used to induce vasoconstriction. For the group that received the norepinephrine, the SMF increased the mean blood flow in the ear lobe (measured by microphotoelectric plethysmography) after 10 min of exposure through to 50 min post-exposure. Likewise, for the group that received the NOS inhibitor, the SMF increased the mean blood flow after 20 min of exposure through to 20 min post-exposure. The SMF also reduced both the norepinephrine-induced and NOS inhibitor-induced high blood pressure 60–100 min post-exposure. When a SMF-exposed group with no pharmacological treatment was compared to a sham exposure group with no pharmacological treatment, no significant differences were found.

This effect was further tested on genetically hypertensive rats [Okano and Ohkubo, 2003b]. At 7 weeks of age, the rats were continuously exposed to a SMF (10 or 25 mT) for 12 weeks. Throughout the 3rd to 5th weeks of SMF exposure, significant antipressor effects on mean blood pressure were found using the tail-cuff method. No differences in mean blood pressure were found between the two MF intensities that were tested. Hormone analysis revealed that the 10 mT SMF (at 5 weeks of exposure) reduced angiotensin II by 65.3% and aldosterone by 39.6%. The 25 mT SMF (at 5 weeks of exposure) reduced angiotensin II by 63.8% and aldosterone by 36.6%. These reductions disappeared at 12 weeks of exposure.

The homeostatic effects of a SMF were again reinforced by Okano et al. [2005a] when they used reserpine (dilate vessels) to induce hypotension and deplete catecholamine reserves in rats. Blood pressure was assessed using the tail-cuff method. The SMF exposure (25 mT, 12 week exposure) significantly reduced the effect of the reserpine, reducing the hypotension caused by the drug. A 10 mT SMF did not have any effect. They concluded that a 25 mT SMF could potentially reduce hypotension in vivo.

Recently, Morris and Skalak [2005] have reported similar findings to Okano et al. [1999, 2005a] and Okano and Ohkubo [2001, 2003a,b]. Using the microvessels of rat skeletal muscle, they found that a SMF (70 mT for 15 min exposure) had a restorative effect on microvascular tone. That is, when vessels had high tone (constricted), the SMF acted to reduce tone, and when the vessels had low tone (dilated), the SMF increased tone. This response was amplified when the vessels had an initial diameter of less than 30 μm (transverse vessels). Intravital microscopy was used to assess vessel tone. The researchers also attempted to detect any response pattern among vessel networks (adjacent vessels, vessel hierarchy, parent/daughter vessels); however, nothing was identified. In a similar conclusion to the above researchers, Morris and Skalak [2005] noted that if a network of vessels is resting at an average tone when SMF exposure occurs, then it is possible that no response to the SMF may be observed. Similarly, if a sample of vessels with heterogeneous tone is exposed to a SMF, it is possible that no net effect will be observed due to the homeostatic action of the SMF.

Okano and Ohkubo [2005a] confirmed the results of Morris and Skalak [2005] when they observed the biphasic and restorative effect of a SMF (5.5 mT) on microvascular tone and blood pressure in conscious rabbits after 30 min of exposure to the neck. Blood pressure and vascular tone were pharmacologically modulated using either norepinephrine and a Ca^{2+} channel blocker (hypertension) or nicardipine (hypotension). The reduction in cutaneous ear lobe microcirculation (measured using microphotoelectric plethysmography) upon application of norepinephrine was significantly attenuated 20–80 min post-exposure to the SMF. A similar, but opposite, SMF effect was observed upon application of nicardipine. By contrast, neither of these effects were observed when the SMF exposure occurred in the pelvic region. The SMF also had an antipressor effect on blood pressure 40–70 min post-exposure to the neck when it was increased by norepinephrine, and the opposite effect 30–50 min post-exposure to the neck when blood pressure was reduced by nicardipine. No effects were observed during or after SMF exposure to the pelvis. The SMF further increased the norepinephrine-reduced baroreflex sensitivity 40–60 min post-exposure to the neck.

Okano and Ohkubo [2005b] thereafter tested the effect of a stronger SMF (180 mT) implanted in the neck of spontaneously hypertensive rats. Hypertensive rats

that were exposed to the SMF (14 weeks) had a mean blood pressure reduction (tail-cuff measurements) of 3.8% in comparison to controls during the 5th–8th weeks of exposure. The SMF also inhibited the decrease in baroreflex sensitivity that was observed in sham animals during the 5th–8th weeks of exposure. When nicardipine (Ca^{2+} channel blocker) was administered to decrease blood pressure, the application of the SMF further enhanced this decrease in mean blood pressure by 6.9% during weeks 1–8 of exposure. These results suggested that the SMF synergistically antagonized Ca^{2+} influx through Ca^{2+} channels. It was also postulated through theoretical calculations that a PEMF modulated by changing heart rate may be effective in altering baroreflex activity.

The effect of high-intensity SMFs, such as those fields used in MRI, has also been investigated. Ichioka et al. [1998] examined the effect of an 8 T SMF on peripheral hemodynamics. They performed an in vivo experiment measuring microvascular and hemodynamic data in the dorsal skin of a rat using intravital microscopy. After 20 min of whole body exposure to the SMF, the MF exposure was stopped. At this time point, vasodilation was apparent and skin microcirculation had increased by 17% at 1 through to 5 min post-exposure. At 10 min post-exposure, blood flow had returned to baseline. The authors suggested that the increase in blood flow post-exposure was due to hyperaemia following reduced flow during the MF exposure. Follow-up work in 2000 by Ichioka et al. again involved whole body exposure of a rat to a strong static field of 8 T for 20 min. In contrast to their previous study, blood flow assessment occurred during exposure. The authors reported that skin microcirculation, measured using laser Doppler flowmetry (a technique based on the Doppler shift of low power laser light scattered by moving erythrocytes), decreased from baseline, and upon cessation of the exposure, blood flow returned to baseline values after 20 min. Although the post-exposure results seem to conflict with the bulk of the studies cited, as well as their study in 1998, the field strength that was tested is substantially higher than most other studies.

Some MF exposure studies have been performed using human subjects. For instance, human exposure to a 0.1 T permanent magnet resulted in no change in skin blood perfusion [Mayrovitz et al., 2001]. Laser Doppler flowmetry and imaging both indicated that no differences in microcirculation existed between groups that received either 36 min of sham or MF exposure. Perfusion measurements were made before and during exposure. These authors emphasized that the lack of MF effect may have been a result of studying healthy subjects with ''normal, unstressed circulation''. Similarly, no significant effect of an 85 mT MF on human skin blood flow was found using laser Doppler flowmetry [Mayrovitz et al., 2005]. When subjects took a deep and rapid inspiration, sympathetic reflexes led to transient vasoconstriction in the skin microvasculature (inspiratory gasp reflex). MF exposure for 20 min did not affect the magnitude of this vasoconstriction. Although this vasoconstriction deviates from ''normal'' resting conditions, the authors suggested that the extent that a tissue/vessel deviates from normality may affect the effect of a MF.

In another experiment, however, Mayrovitz and Groseclose [2005] did find an effect of a 0.4 T SMF on skin microcirculation of human subjects. A sham magnet was placed under the 2nd finger and another placed under the 4th finger for a period of 15 min. Next, a sham magnet was again placed under the 4th finger and an active magnet (of either polarity) was placed under the 2nd finger for 15 min. This process was repeated for another 15 min using a magnet of the opposite polarity under the 2nd finger. A significant reduction in skin blood flow using laser Doppler flowimetry was reported after three 15 min exposure intervals using magnets of either polarity. Polarity of the magnet had no effect.

Time-Changing Magnetic Fields

Few researchers have examined the use of pulsed electromagnetic fields (PEMFs) on microcirculation and mircovasculature. Smith et al. [2004] used a PEMF (positive rate of change of 18.8 T/s; negative rate of 8 T/s) to examine acute changes in arteriole diameter in the cremaster muscle of the rat using intravital microscopy. The particular PEMF that was used is clinically useful for the healing of non-union fractures. Their experiment revealed that a 2 min local exposure to the PEMF led to a 9% increase in arteriole diameter. Subsequent exposure to the same PEMF for 60 min led to an 8.7% increase in arteriolar diameter. Temperature and systemic hemodynamics were ruled out as confounding variables, and no differences were found between small and large vessels.

A study by Schuhfried et al. [2005] also explored the effect of two low frequency PEMFs on the cutaneous microcirculation of human volunteers. A low-dose PEMF (0.1 mT, 30 Hz, Bemer specific signal), high-dose PEMF (8.4 mT, 10 Hz, sine wave pulses), and sham MF were each randomly applied to the entire foot (double-blind) for one 30 min exposure session each separated by 1 week intervals. A laser Doppler probe was placed on the dorsum of the foot and measurements were made prior to each PEMF exposure, every 5 min during the half-hour exposure period, and then 5 and 10 min post-exposure. There were no reported changes

in microcirculation (or skin temperature) after either PEMF exposure session. Schuhfried et al. [2005] note that the lack of effect may be due to the single, short-term application of the PEMF; however, Smith et al. [2004] had a comparably short exposure period and did find an effect of a PEMF on microcirculation. Other PEMF parameters did however differ, as did the tested species.

A number of studies have examined radiofrequency MFs on microcirculation and microvasculature. One of the first reports of non-thermal vasodilation by electromagnetic radiation was made by Miura and Okada [1991]. They exposed the arterioles in the web of a frog to radiofrequency burst-type EMF radiation of various parameters. Dilation was measured using a video microscope gauge. Vasodilation occurred slowly (in arterioles that had been constricted by norepinephrine and in non-stimulated vessels), reached a plateau after 60 min of MF exposure, and then continued for 40–100 min after MF exposure was ceased. A 10–100 MHz frequency (compared to 1 MHz), 50% burst time (compared to 10, 30, 70, 90, 100%), and 10 kHz burst rate (compared to 10^2, 10^3, 10^5, 10^6 Hz) produced the greatest vasodilatory effect. These other burst times and burst rates also produced vasodilation; however, significance levels were not included in the study. It was also found that the concentration Ca^{2+} in the perfusion solution (Ringer's solution) influenced the extent of vasodilation (low Ca^{2+} increased vasodilation). Inhibiting Ca^{2+}-ATPase eliminated the MF-induced vasodilation. It was concluded that the MF effect involved modulation of Ca^{2+} outflow through the cell membrane or an increase in Ca^{2+} uptake by the sarcoplasmic reticulum.

Another early study, by Ueno et al. [1986], reported a decrease in human skin microcirculation when exposed for 60 s to an alternating MF (32 and 48 mT, 3.8 kHz). A rapid decrease in blood flow, measured using laser Doppler flowimetry, was observed 6–8 s after the start of exposure, and values returned to normal after 10 s. The authors suggested that the body responds to MF exposure with a ''defense'' or ''escape'' reaction, namely, vasoconstriction of the vessels in the skin. Ueno et al. [1986] concluded that the MF effect is mediated by the nervous system, specifically, the cortico-hypothalamico-bulbar system.

Similarly, Mayrovitz and Larsen [1992] investigated the effect of a PEMF (27.12 MHz, 600 pulses/s) on human skin microcirculation. A laser Doppler probe was placed on both forearms of healthy volunteers, and the coil producing the MF was placed directly above the probe on one forearm. The values obtained during the 45 min exposure period were compared to the 20 min of baseline measurements. It was found that 40 min into the MF exposure, blood perfusion had significantly increased in the exposed arm (by 29%) and perfusion was unchanged in the control arm. Importantly, the researchers also measured skin temperature in both arms: starting at 5 min into the MF exposure, skin temperature on the exposed arm was significantly higher than on the control arm. It was not clear to these researchers whether it was the temperature increase that caused in the increase in perfusion or whether the increase in temperature was a result of MF effect on muscle blood flow. Further use of this pulse sequence (27.12 MHz, 600 pulses/s, 0.1 mT) indicated that it was effective in increasing blood perfusion in peri-ulcer skin microcirculation of diabetic patients [Mayrovitz and Larsen, 1995]. A number of these patients also had lower extremity arterial disease. A laser Doppler probe was placed on the peri-ulcer skin of either the toe or foot (subjects had an ulcer in one of these two locations) and also on the contralateral limb. The coil generating the MF was placed directly above the ulcer. It was found that during the last 5 min of the 45 min exposure period perfusion had significantly increased at the peri-ulcer site compared to the control limb site. There was no corresponding increase in skin temperature. Another important finding of this experiment was that prior to MF exposure the ulcer site had higher perfusion and blood volume than the non-ulcerated site, yet the MF was still able to induce further increases. These researchers suggested that new microvessel recruitment is likely responsible for the increases in perfusion and volume after exposure since there was no change in blood velocity after exposure.

Addressing the concern over the safety of cellular phone use, Monfecola et al. [2003] examined the effect of non-ionizing electromagnetic radiation (3×10^8 to 3×10^{11} Hz) on cutaneous microcirculation of human volunteers. They reported that blood flow (in the ear skin), measured using laser Doppler flowmetry, was increased by 131.74% from baseline when the cellular phone was turned on and pressed against the ear. When the cellular phone was turned on, pressed against the ear, and was receiving a signal, the blood flow was increased by 157.67% from the baseline. This increase in blood flow could not solely be attributed to a thermal effect due to skin contact with the phone; when the subjects had the phone pressed against their ear and the phone turned off, there was only a 61.38% increase in blood flow from baseline. The authors concluded that the electromagnetic radiation from cellular phones does indeed lead to a significant modification of microcirculation in the cutaneous tissue of the ear.

This appears to correspond with the early results obtained by Miura and Okada [1991] involving RF MFs. Similarly, Huber et al. [2002] reported that a

900 MHz pulse-modulated EMF used in cellular phones led to an increase in regional cerebral blood flow. Subjects were exposed unilaterally (only the left side) to the MF for 30 min while sitting with their heads between two antennas. Ten min after this exposure, the conscious human subjects received a positron emission tomography (PET) scan. Blood flow was increased in the dorsolateral prefrontal cortex only on the side ipsilateral to exposure. This region of the brain is strongly linked to working memory.

In contrast to the previous two findings, Haarala et al. [2003] concluded that a pulsed radio-frequency EMF associated with mobile phones (902 MHz, pulse rate 217 Hz) did not have an effect on regional cerebral blood flow in the brain area exposed to the maximum EMF. Human subjects had a phone fastened to one side of their head and were exposed to the EMF for 45 min while being imaged by a PET scanner for 90 min. It is, however, possible that EMF effects may have occurred in other regions of the brain. Tsurita et al. [2000] also reported that an EMF used in cellular phones (1439 MHz time division multiple access) did not produce an effect in their experiment. Non-anesthetized rats were exposed to the EMF for 1 h a day (for either 2 or 4 weeks) by being confined in tube with their heads directed toward the exposure apparatus. After 2 or 4 weeks, rats were placed under anesthesia (diethylether and sodium pentobarbital) and staining methods were employed to determine the effect of MF exposure on the permeability of the blood-brain-barrier (BBB). No changes were found after 2 or 4 weeks. These MF-exposed rats were compared to sham-exposed rats and also to rats that had not been confined within the exposure apparatus.

It would appear that ten studies (four using a SMF, six using a time-varying MF) support the finding that MFs act to increase blood flow, and three (two using a SMF, one using a RF MF) support a negative finding. Ten studies, all using a SMF, found a homeostatic effect of MF exposure. Four studies found no effect. There does not appear to be a clear pattern in terms of why one experiment produces an increase and another, a decrease in blood flow/pressure. Conflicting effects were found using MFs of similar parameters; however, different subjects types and test sites (e.g., skin, muscle, tail vessels) were used. All of the studies that reported a decrease in blood flow/pressure used healthy subjects, so this decrease was not a result of an initially high blood flow/pressure or a diseased state. Two of these studies used conscious subjects and one used anesthetized subjects (urethane). In the studies that reported an increase in blood flow/pressure, all studies used healthy subjects (both humans and animals). Half used anesthetized subjects, using either pentobarbital sodium or urethane, and the other half, conscious subjects. An overview of the results of these studies can be found in Table 1.

MECHANISM OF ACTION/CELLULAR EFFECTS OF MF EXPOSURE

The mechanisms by which MFs exert their effects are still relatively unknown. There are various theories to account for the microcirculatory changes following MF exposure.

The biological effects of MFs have often been linked to nitric oxide (NO). For instance, Kavaliers et al. [1998] found that NO and NOS were implicated in the effects of extremely low frequency (ELF) MFs on opioid-induced analgesia in land snails. Many believe that NO may also be the molecule responsible for the changes in vessel diameter following MF exposure.

Static Magnetic Fields and Nitric Oxide

An investigation by Okano et al. [2005b] indicates that the homeostatic effect of MFs might influence NO pathways. When genetically hypertensive rats were exposed to a SMF (1 or 5 mT) for 12 weeks, blood pressure, the concentration of NO metabolites, angiotensin II, and aldosterone were reduced. Specifically, exposure to the SMF reduced blood pressure during weeks 3–6. Hypertensive rats are known to have increased levels of NO metabolites, likely due to the upregulation of NOS. Exposure to the 5 mT SMF for 6 weeks significantly reduced the concentration of NO metabolites by 73.2%. The 1 mT SMF did not have an effect on the NO metabolites. At 3 weeks, the 5 mT SMF reduced angiotensin II by 51.1% and aldosterone by 40.2%, and at 6 weeks reduced angiotensin II by 58.2% and aldosterone by 72.2%. Similar significant reductions in angiotensin II and aldosterone were seen with the 1 mT field. At 12 weeks, all effects on the NO metabolites, angiotensin II, and aldosterone disappeared.

Other research by these investigators, however, reports a lack of change in measured NO upon MF exposure. Okano et al. [2005a] used a SMF (10 and 25 mT) to counter reserpine-induced hypotension in rats. They reported that the SMF did significantly counter the reserpine-induced effects; however, this effect was not mediated by NO. They found no significant differences in the concentration of NO metabolites between any tested groups. In another experiment, Okano and Ohkubo [2005a] reported similar findings. After exposing conscious rabbits to a 5.5 mT SMF for 30 min, they

TABLE 1. MF Effects on Microcirculation and Microvasculature

Study	Parameters	Experimental specimen	MF effects
Xu et al. [2001]	0.3, 1, and 10 mT (SMF); 0.3 and 1 mT (50 Hz EMF); 10 min whole body exposure	Anesthetized mice (tibialis anterior muscle)	↑ Blood velocity (1 and 10 mT SMF) (during and post-exposure); ↑ blood velocity (1 mT EMF) (post-exposure)
Okano et al. [1999]	1 mT (SMF); 10 min local exposure	Conscious rabbits (cutaneous tissue of ear)	When ↑ vascular tone: vasodilation (↑ blood flow) (post-exposure); when ↓ vascular tone: vasoconstriction (↓ blood flow) (during and post-exposure)
Okano and Ohkubo [2001]	1 mT (SMF); 30 min local exposure	Conscious rabbits (cutaneous tissue of ear)	When ↑ vascular tone: ↓ BP and ↑ blood flow (during and post-exposure); when ↓ vascular tone: ↑ BP and ↓ blood flow (during exposure)
Okano et al. [2005b]	1 and 5 mT (SMF); 12 weeks continuous whole body exposure	Conscious hypertensive rats (vessels in tail)	↓ BP (during exposure)
Ohkubo and Xu [1997]	1, 5, and 10 mT (SMF); 10 min whole body exposure	Conscious rabbits (cutaneous tissue of ear)	When ↑ vascular tone: vasodilation (during exposure); when ↓ vascular tone: vasoconstriction (during exposure)
Okano and Ohkubo [2003a]	5.5 mT (SMF); 30 min whole body exposure	Conscious rabbits (cutaneous tissue of ear)	When ↑ vascular tone: ↓ BP and ↑ blood flow (during and post-exposure)
Okano and Ohkubo [2005a]	5.5 mT (SMF); 30 min exposure to the neck or pelvis	Conscious rabbits (cutaneous tissue of ear)	When ↑ vascular tone: ↓ BP and ↑ blood flow (post-exposure to neck only); when ↓ vascular tone: ↑ BP and ↓ blood flow (post-exposure to neck only); when ↓ baroreflex sensitivity: ↑ baroreflex sensitivity (post-exposure)
Okano and Ohkubo [2003b]	10 and 25 mT (SMF); 12 weeks continuous whole body exposure	Conscious hypertensive rats (vessels in tail)	↓ BP (during exposure)
Okano et al. [2005a]	10 and 25 mT (SMF); 12 weeks continuous whole body exposure	Conscious hypotensive rats (vessels in tail)	When ↓ BP: ↑ BP (during exposure)
Morris and Skalak [2005]	70 mT (SMF); 15 min local exposure	Anesthetized rats (skeletal muscle microvessels)	When ↑ vascular tone: ↓ vascular tone (post-exposure); when ↓ vascular tone: ↑ vascular tone (post-exposure)
Mayrovitz et al. [2005]	85 mT (SMF); 20 min local exposure	Conscious humans (cutaneous tissue of middle finger)	No effect (during exposure)
Mayrovitz et al. [2001]	0.1 T (SMF); 36 min local exposure	Conscious humans (cutaneous tissue of index finger)	No effect (during exposure)
Okano and Ohkubo [2005b]	0.18 T (SMF implanted in neck); 14 weeks continuous exposure	Conscious hypertensive rats	↓ BP (during exposure); ↑ baroreflex sensitivity (during exposure)
Gmitrov et al. [2002]	0.25 T (SMF); 40 min local exposure	Anesthetized rabbits (cutaneous tissue of ear lobe)	↑ Blood flow (during and post-exposure)
Gmitrov [2004]	0.35 T (SMF); 40 min local exposure	Conscious rabbits (cutaneous tissue of ear lobe)	↑ Blood flow (post-exposure); ↑ baroreflex regulation (post-exposure)
Mayrovitz and Groseclose [2005]	0.4 T (SMF); three 15 min local exposure intervals	Conscious humans (cutaneous tissue)	↓ Blood flow (during exposure)
Ichioka et al. [1998]	8 T (SMF); 20 min whole body exposure	Anesthetized rats (cutaneous dorsal tissue)	↑ Blood flow (post-exposure)

Continues on following page

TABLE 1. (*Continued.*)

Study	Parameters	Experimental specimen	MF effects
Ichioka et al. [2000]	8 T (SMF); 20 min whole body exposure	Anesthetized rats (cutaneous dorsal tissue)	↓ Blood flow (during exposure)
Schuhfried et al. [2005]	0.1 and 8.4 mT (PEMF); 30 min whole foot exposure	Conscious humans (cutaneous tissue of foot)	No effect of PEMF
Smith et al. [2004]	PEMF (+ve amplitude of 18.8 T/s; −ve amplitude of 8 T/ s); 2 and 60 min local exposure	Anesthetized rats (cremaster muscle)	↑ Arteriolar diameter (post-exposure)
Ueno et al. [1986]	EMF (32 and 48 mT, 3.8 kHz RF); 60 s local exposure	Conscious humans (cutaneous tissue of finger-tip)	↓ Blood flow (during exposure)
Miura and Okada [1991]	Burst-type EMF (10 MHz RF, 0.73 μT, 10 kHz burst rate, 50% burst time); 60 min local exposure	Anesthetized albino frogs (web microcirculation)	↑ Blood flow (during and post-exposure)
Mayrovitz and Larsen [1992]	PEMF (27.12 MHz RF, 600 pulses/s); 45 min local exposure	Conscious humans (cutaneous tissue of forearm)	↑ Blood flow (last 5 min of exposure)
Mayrovitz and Larsen [1995]	PEMF (27.12 MHz RF, 600 pulses/s, 0.1 mT); 45 min local exposure	Conscious humans (peri-ulcer cutaneous tissue)	↑ Blood flow (last 5 min of exposure)
Huber et al. [2002]	EMF (900 MHz RF); 30 min local exposure	Conscious humans (brain)	↑ blood flow (post-exposure)
Haarala et al. [2003]	EMF (902 MHz RF); 45 min local exposure	Conscious humans (brain)	No effect (during exposure)
Monfecola et al. [2003]	EMF (3×10^8 to 3×10^{11} Hz RF); 12 min local exposure	Conscious humans (cutaneous tissue of ear)	↑ Blood flow (during exposure)

EMF: Electromagnetic fields. EMFs are waves composed of both electric and magnetic fields.
PEMF: Pulsed electromagnetic field. A MF that is pulsed on and off at a specific frequency and intensity.
RF: Radiofrequency. Frequency = 3 kHz–300 GHz.
SMF: Static magnetic field. A direct current MF that does not vary with time (0 Hz) and has an infinitely long wavelength.
Note: It is not clear from the articles cited whether the MF strengths listed for the AC fields are peak or rms values.

reported biphasic effects on pharmacologically modified vessel tone and blood pressure, but no changes in NO metabolites. They suggested that the site of SMF interaction may be biochemical mechanisms involving baroreflex sensitivity and signal transduction pathways involving Ca^{2+}.

The above findings were partially elucidated when spontaneously hypertensive rats were exposed to a 180 mT SMF (magnet implanted in neck) for 14 weeks [Okano and Ohkubo, 2005b]. The SMF enhanced the hypotensive effect of nicardipine and caused a further increase in NO metabolites during the 6th–8th week of exposure compared to rats that also received nicardipine but were exposed to a sham MF. Thus, the synergistic effect of the SMF appeared to be related to NO. The SMF alone (without nicardipine), however, did not induce any change in NO metabolite concentration.

Mnaimneh et al. [1996] also reported that inducible NO production in macrophages taken from mice was not increased by the particular MF parameters that they used. They tested a SMF of 1, 10, 50, and 100 mT (plus an ambient 50 Hz MF) and a sinusoidal MF of 1.6 mT (1 Hz). In spite of their results, Mnaimneh et al. [1996] made note that MFs could potentially modify a NO-dependent reaction that is independent of, or ''down-stream'' from, NO formation.

Time-Changing Magnetic Fields and Nitric Oxide

Noda et al. [2000] proposed that PEMFs may exert their effects by affecting the activity of NOS. In their experiment, rat brain tissue was divided up into seven regions and each sample was homogenized. Next, they passed a 0.1 mT pulsed DC (direct current) field through each of the homogenized brain samples for 1 h. A significant increase in NOS activity was found in the cerebellum only and not in the other six regions tested. Likewise, Yoshikawa et al. [2000] found that when mice were injected with lipopolysaccharide (a bacterial stressor) for the induction of inducible nitric oxide synthase (iNOS), exposure to an EMF (0.1 mT, 60 Hz) for 5.5 h enhanced the generation of NO in the liver. Exposure to the EMF alone, with no lipopolysaccharide, did not result in an increase in NO generation. Yoshikawa et al. [2000] suggested that EMFs may exert

their effects by extending the life of free radicals and altering signal transduction pathways involved with iNOS induction.

Miura et al. [1993] used tissue from rat cerebellum to determine whether the vasodilation due to radio-frequency burst-type EMF radiation that they had observed in previous studies was related to NO synthesis. They studied the cerebellum since NO synthase is predominant in this region. The authors concluded that after 30 min of exposure to a 2.65 μT MF with a 10 MHz frequency and a 10 kHz burst rate, NO did gradually increase to a maximal value after 20 min cessation of exposure. This effect was near abolished using a NOS inhibitor. Cyclic guanosine monophosphate (cGMP) was also increased when tissue was exposed to EMF radiation. When a cGMP inhibitor was used, the effect of the radiation was abolished.

A lack of effect on NO was found when a PEMF (0.4 mT, 120 Hz, sinusoidal) was tested by Kim et al. [2002]. They found no differences between a control and PEMF-exposed group in neuronal NOS (nNOS) expression in an injured recurrent rat laryngeal nerve.

It is clear that conflicting evidence involving MFs and NO has been obtained. The limited studies that have been performed measure NO in various tissues and use MFs of varying strengths and frequencies. It is therefore difficult to make any conclusions on this subject. The role of NO as a mediator for the biological effects of MF exposure is uncertain. More research is required to elucidate this debate.

Other radicals within the body, in addition to NO, may be influenced by MF exposure. Specifically, it is known that high concentrations of reactive oxygen species are involved with reperfusion injury, which is the harm that occurs to tissue when blood flow is reestablished after ischemia. It has been found that stress proteins protect tissue from this type of injury and that MF exposure can induce a stress response that also exerts a protective effect [DiCarlo et al., 1999; Carmody et al., 2000]. In light of this interaction, it is plausible that MFs could interact with other radicals as well.

Magnetic Field Effects on Blood Vessels

Some research indicates that MFs can influence vessel growth and development. For instance, some research on ulcers and MF therapy has partly linked the enhanced healing of wounds to effects on microcirculation and microvasculature. Any study that involves MF effects on microvessel growth or development has been included in this section. Studies are organized by modality (SMFs followed by time-changing MFs).

A SMF (0.2 T) was applied to the chorioallantoic membranes of chick embryos for 3 h to test the effect of exposure on angiogenesis [Ruggiero et al., 2004]. Sponges containing either prostaglandin E1 or fetal calf serum were placed on the membranes to induce angiogenesis; phosphate buffered solution was used as a negative control. Two days after real or sham exposure for 3 h, the membranes were examined for the presence of new microvessels. Both sham groups that were treated with either prostaglandin E1 or fetal calf serum exhibited a strong angiogenic response. The SMF-exposed groups, however, exhibited reduced angiogenesis with fewer new vessels developing towards the sponges.

The above effect, however, has not been consistently replicated. In a study involving the use of MFs to treat ulcers not responsive to conventional treatments, exposure led to an increase in the superficial vascular network of the skin [Cañedo-Dorantes et al., 2002]. They used a SMF (approximately 52 mT) combined with an ELF MF (3.7 mT, 60 Hz) that consisted of frequencies that could interact with peripheral blood mononuclear cells (cells that promote the healing of ulcers). The MF exposure was localized to one arm 2–3 h/day 3 times a week. After the exposure, it was found that 69% of the 42 chronic arterial and venous leg ulcers were cured or substantially healed. The improvement in the arterial ulcers was partly attributed to an increase in the superficial vascular network (after 4–8 weeks of treatment), and the improvement in the venous ulcers was partly attributed to reduced/eliminated edema (after 3–6 weeks of treatment). This study, however, used a before-after design that did not compare MF treatment to a control. It is therefore difficult to ascertain whether the effects on vascularization and reduction of edema are enhanced by the MF or are simply a result of time or some other factor.

An ELF MF (50 Hz, 8 mT peak) was used in an attempt to improve the healing of skin wounds surgically created on the backs of rats [Ottani et al., 1988]. Thirty minutes of MF exposure immediately after surgery and every 12 h thereafter for 42 days, led to a greater and faster rate of healing. Specifically, the exposed animals had developed a new vascular network on the 6th day after surgery; whereas, this occurred in the controls 12 days post-surgery. At the 12 days post-surgery mark for the exposed animals, a rich capillary network had formed. These differences were evaluated by light and electron microscopy. Increased angiogenesis in response to a PEMF (0.1 mT, 15 Hz) was also observed in vitro using human umbilical vein and bovine aortic endothelial cells [Yen-Patton et al., 1988]. A wound model was created by raking a comb across a monolayer of endothelial cells. As a result of the continuous PEMF exposure, there was a 20–40% significant increase in the growth rate of the endothelial cells, and these cells appeared more elongated in appearance, forming 10–30% more "sprouts" than controls. When a 2nd set

of human umbilical vein endothelial cells were disrupted and separated from each other, PEMF exposure led to vascularization within hours; this took 1–2 months with non-exposed cells. The stages of neovascularization that occurred in this experiment were similar to the stages that occur in vivo.

In another experiment, the effect of three PEMF waveforms on blood vessel growth in the ears of a rabbit model was investigated [Greenough, 1992]. A 15 Hz pulse burst waveform (6 h daily for 25 days) led to an increased rate of vascular growth at day 24, but no significant changes in the maturation of the vessels compared to controls. The 2nd pulseform (72 Hz, single pulse, 1 h daily for 25 days) had no effect on the growth rate, but did significantly enhance the maturation of the vessels at day 24. The 3rd pulseform (72 Hz, single pulse, 6 h daily) led to no significant effects.

Weber et al. [2004] tested the effects of a PEMF (0.1 mT, 65-μs burst of 27.12 MHz sinusoidal waves) on angiogenesis using two different exposure lengths (8 or 12 weeks). They created a groin composite flap in rats by removing a portion of tail artery that was then anastomosed to two other arteries. This arterial loop was placed over the abdominal wall and under the skin. Rats received MF exposure twice daily (exposures were at least 4 h apart) for 30 min each exposure. After either 8 or 12 weeks, rats underwent a 2nd surgery to ligate the vessel that was initially responsible for blood flow to the composite flap. The tissue would then be supplied only by the neoarterial loop. Five days later, the percentage of flap survival was calculated. The group exposed to the PEMF for 8 weeks had significant skin flap survival whereas the skin flap in the control group did not survive. The group exposed to the PEMF for 12 weeks did not differ significantly from the control group. This research indicates that it is possible to accelerate angiogenesis using PEMFs.

Roland et al. [2000] performed a similar experiment using a microsurgically transferred vessel in rats. An arterial loop, consisting of tail artery, was anastomosed to the femoral artery and was placed over the groin musculature. A PEMF (0.01 or 0.2 mT, 2–20 ms pulses, 27.12 MHz) was applied twice daily for 30 min at each exposure session. Surface area neovascularization was measured after either 4, 8, or 12 weeks of MF exposure. At all time points, both MF-treated groups exhibited significantly more neovascularization than the controls. There were no differences between the two MF-exposed groups. This study clearly indicates that under the correct conditions MF exposure can increase blood vessel development and growth.

Tepper et al. [2004] also used a PEMF (1.2 mT, 15 Hz, asymmetric 4.5 ms pulses) both in vitro and in vivo to test its effect on angiogenesis. After human umbilical vein endothelial cells were exposed to the MF for 7–10 days, there was sevenfold increase in the degree of cell tubulization compared to sham-exposed cells. There was also a significant increase in the proliferation of PEMF-exposed endothelial cells. This increase was similar to what would be expected after a large dose of vascular endothelial growth factor. An interesting finding of this experiment was that fibroblast and osteoblast cell lines did not show the same proliferation as did the endothelial cells. It was proposed that endothelial cells are the main target for PEMFs by releasing proteins that upregulate angiogenesis. This is an important finding for the healing of fractures, in that perhaps the MFs interact with vascularity instead of osteogenesis [Tepper et al., 2004]. It was also found that when a gel that supports vascular growth was implanted subcutaneously into mice, the PEMF exposure (8 h/day) stimulated significantly more (more than twofold) vascular growth than did sham exposure after 3, 10, and 14 days.

In contrast to the previous few studies, Williams et al. [2001] found that a PEMF (10, 15, or 20 mT) reduced the vascularization of breast tumors implanted into mice. A half sinewave MF with 120 pulses/s was used. Seven days after tumor implantation, whole body MF treatment was initiated 10 min daily for 12 days. MF exposure led to a significantly greater degree of expression of CD31 (platelet endothelial cell adhesion molecule), a marker for blood vessels. Specifically, the group exposed to the 10 mT MF had a 39% decrease in CD31 staining compared to controls, whereas the 15 mT group had a 68% decrease and the 20 mT group a 62% decrease. These authors concluded that since there were no significant differences between the 15 and 20 mT MF groups, that a biological window exists within this range of amplitudes.

It is inferred that additional vessel growth leads to greater circulation, although blood flow was not measured in any of the above experiments. Seven of these studies (one using a SMF and six using a time-varying MF) reported an increase in angiogenesis and two reported a decrease (one using a SMF and the other a time-varying MF). Again, there do not appear to be any features that distinguish between these varying results. An overview of the results of these studies can be found in Table 2.

EFFECT OF ANESTHETICS ON MICROCIRCULATION AND MICROVASCULATURE

Most, if not all, in vivo animal experiments involving the effects of MF exposure on microcirculation and microvasculature are performed under anesthesia. Not surprisingly, anesthetics can have a number

TABLE 2. Cellular Effects of MFs

Study	Parameters	Experimental specimen	MF cellular effects
Mnaimneh et al. [1996]	1, 10, 50, 100 mT (SMF); sinusoidal (1.6 mT, 1 Hz); 14 h exposure	Activated macrophages from mice	No change in iNOS expression
Okano and Ohkubo [2003b]	10 and 25 mT (SMF); 12 weeks continuous whole body exposure	Blood samples from hypertensive rats; (jugular vein)	↓ Angiotensin II and aldosterone (during exposure)
Okano et al. [2005a]	10 and 25 mT (SMF); 12 weeks continuous whole body exposure	Blood samples from normotensive and hypotensive rats (jugular vein)	No change in NO metabolites
Okano et al. [2005b]	1 and 5 mT (SMF); 12 weeks continuous exposure	Blood samples from hypertensive rats (jugular vein)	↓ NO metabolites, angiotensin II and aldosterone (during exposure)
Okano and Ohkubo [2005a]	5.5 mT (SMF); 30 min exposure to the neck or pelvis	Blood samples from rabbits (central artery of ear lobe)	No change in NO metabolites
Cañedo-Dorantes et al. [2002]	52 mT (SMF) + 3.7 mT, 60 Hz (ELF MF)	Human leg ulcers (skin) not responsive to normal treatment	Superficial vascular network became visible; reduced edema
Okano and Ohkubo [2005b]	180 mT (SMF implanted in neck); 14 weeks continuous exposure	Blood samples from hypertensive rats (jugular vein)	No change in NO metabolites; ↑ NO metabolites when SMF was applied with nicardipine
Ruggiero et al. [2004]	0.2 T (SMF); 3 h whole-egg exposure	Chorioallantoic membrane in chick embryos	↓ Angiogenesis
Roland et al. [2000]	PEMF (0.01 or 0.2 mT, 27.12 MHz); 30 min whole body exposure twice daily for 4, 8, or 12 weeks	Blood vessels in rat subcutaneous tissue	↑ Rate of vascular growth
Yen-Patton et al. [1988]	PEMF (0.1 mT, 15 Hz); continuous exposure	Human and bovine endothelial cells	↑ Growth rate of endothelial cells; cells more elongated; more sprouts
Yoshikawa et al. [2000]	0.1 mT, 60 Hz; 5.5 h exposure	Liver of mice	↑ NOS
Weber et al. [2004]	0.1 mT, 27.12 MHz; 30 min whole body exposure twice daily for 8 or 12 weeks	Blood vessels in rat subcutaneous tissue	↑ Angiogenesis
Noda et al. [2000]	PEMF (0.1 mT, DC); 60 min exposure	Homogenized rat brain	↑ NOS in cerebellum
Kim et al. [2002]	PEMF (0.4 mT, 120 Hz, sinusoidal); 4 h/day, 5 days/week, 12 weeks	Injured recurrent laryngeal nerve of rats	No change in nNOS expression
Tepper et al. [2004]	PEMF (1.2 mT, 15 Hz, asymmetric 4.5 ms pulses)	Human umbilical vein endothelial cells (7–10 days continuous exposure); transgenic mice (8 h/day whole body exposure for 3, 10, or 14 days)	↑ Rate of endothelial cell tubulization and proliferation; ↑ angiogenesis
Ottani et al. [1988]	PEMF (8 mT peak, 50 Hz); 30 min whole body exposure every 12 h for 42 days	Skin wounds in rats	↑ Rate of vascular network development
Williams et al. [2001]	PEMF (10, 15, and 20 mT, 120 pulses/s, half sinewave)	Breast tumors (murine 16/C mammary adrenocarcinoma cells) in mice	↓ Angiogenesis in tumors
Greenough [1992]	PEMF (15 and 72 Hz); 1 or 6 h daily for 25 days	Blood vessels in rabbit ears	↑ Rate of vascular growth (15 Hz, 6 h daily); enhanced vessel maturation (72 Hz, 1 h daily)
Miura et al. [1993]	Burst-type (2.65 μT, 10 MHz RF, 10 kHz burst rate); 30 min exposure	Rat cerebellum supernatant	↑ NO; ↑ cGMP

of effects on the various organ systems; the cardiovascular and microcirculatory systems are no exception. It has been shown by Longnecker and Harris [1980] that in the laboratory anesthetics can skew results by altering regional blood flow, response to vasoactive chemicals, and response to neural input. In general, deep anesthesia leads to vasodilation of the arterioles and venules, diminished response to vasoactive compounds, and decreased erythrocyte velocity within the capillaries [Longnecker and Harris, 1980]. To further confound matters, each anesthetic alters the microcirculation in a slightly different manner.

The choice of anesthetic agent used by researchers is variable. In this review, the most popular choices were ketamine, pentobarbital, and urethane. Another commonly used anesthetic is propofol. In an experiment by Gustafsson et al. [1995], the effects of three popular anesthetics on skeletal muscle capillary and regional blood flow were compared. This study indicated that ketamine maintained capillary perfusion the best, followed by pentobarbital and then propofol.

Ketamine is a dissociative anesthetic that is restricted to veterinary use. It provides fast, intense analgesia by inhibiting excitatory synaptic transmission at N-methyl-D-aspartate (NMDA) receptors. Ketamine imposes certain effects on the cardiovascular system, including increased systemic and pulmonary arterial blood pressure, heart rate, cardiac output, myocardial oxygen consumption, coronary blood flow, and cardiac work (Weinberg, 1997, p 26). Studies involving changes in perfusion should take note that ketamine is a potent cerebral vasodilator that increases blood flow to the brain and intracranial pressure (Weinberg, 1997, p 26). It should also be noted that ketamine causes vasodilation in tissues that are primarily innervated by α-adrenoceptors, and in contrast, ketamine causes vasoconstriction in tissues that are mainly innervated by β-adrenoceptors (Vickers et al., 1984, p 63). Furthermore, in the peripheral system, ketamine is a vasodilator (Kaufman and Taberner, 1996, p 69) with arteriolar vasodilation of 25% [Longnecker and Harris, 1980].

Pentobarbital belongs to the class of anesthetics known as the barbiturates. The barbiturates cause a decrease in systemic arterial pressure and cardiac output, and an increase in heart rate. They tend to lead to hypotension due to venodilation and the pooling of blood in the periphery (Weinberg, 1997, p 18). Longnecker and Harris [1980] state that subcutaneous venules dilate 15% and arterioles dilate 25%. The drop in blood pressure observed at large doses of barbiturates is due in part to direct effects on the musculature of arterioles (Vickers et al., 1984, p 102).

Propofol is a rapid-acting anesthetic that interacts with gamma-aminobutyric acid ($GABA_A$) receptors to enhance inhibitory synaptic transmission. It is most rapidly distributed to the tissues with the most vasculature (McCaughey et al., 1997, p 186). Propofol is a cardiovascular depressant that causes a 20–30% reduction in systolic blood pressure and a 20% decrease in systemic vascular resistance (Kaufman and Taberner, 1996, p 71). In the peripheral system, propofol causes noticeable decrease in vascular resistance which leads to systemic hypotension (McCaughey et al., 1997, p 187).

Urethane is an anesthetic used in veterinary medicine and animal experiments. It has minimal effects on the cardiovascular and respiratory systems [Hara and Harris, 2002]. Urethane has, however, been shown to decrease blood pressure by 30% and this effect can last for 30 min [Longnecker and Harris, 1980]. Dilation by 15% occurs in the arterioles, particularly the second-order arterioles (the first set of arterioles that branch off the central arteriole), and the venules appear to be unaffected [Longnecker and Harris, 1980].

As mentioned previously, the studies compared in this review use a variety of anesthetics. This may or may not be problematic. In each study where experimental groups (receiving MF exposure) were compared to a control group, all groups received the same anesthetic; thus, any side effects from the anesthetic were experienced by all groups and therefore should cancel out. However, no experiments have been performed to determine whether the anesthetic's mechanism of action is affected in any way by the MF. In any particular experiment where perfusion is affected by MF exposure, there is no evidence to determine whether it is the MF that is affecting the physiology associated with perfusion/blood flow or whether the MF has exacerbated or diminished a particular anesthetic side effect on perfusion. This point may simply be a fine detail, contributing little to an overall effect, or it could become quite significant if MF therapy was 1 day to be used in a clinical setting on non-anesthetized patients. Also, if a particular anesthetic caused vasodilation or vasoconstriction, it is possible that the true extent of a MF effect on vessel diameter might not be realized since the vessel is already at its maximum or minimum diameter due to the anesthetic.

DISCUSSION

Research on the effects of MFs on microcirculation and microvasculature is limited, but growing. Not only is research in this domain important for the discovery of potential medical therapies, but also the importance of establishing accurate safety standards surrounding MF exposure is obvious.

A common problem with pharmaceutical drugs is that they often exert their effects at sites within the body other than the target site [Goodwin and Meares, 2001]. Localization of a drug to a particular tissue is difficult to achieve. For instance, the popular drug Viagra® (sildenafil citrate), used for erectile dysfunction, increases blood flow to the corpus carvernosum by inhibiting phosphodiesterase type 5 (PDE-5) [Raja and Nayak, 2004]. Unfortunately, this effect is not limited to the corpus carvernosum; PDE-5 is also located in smooth muscle, skeletal muscle, and platelets. Therefore, some side effects of Viagra® include hypotension and effects on the central nervous and muscoskeletal systems [Cheitlin et al., 1999]. A similar example would be the problem of isolating the drugs used for chemotherapy and radioimmunotherapy to the target organ/tumor site, without causing toxicity to other organs or metabolism or excretion by the liver and kidneys [Goodwin and Meares, 2001]. The ability to alter microcirculation to a particular, isolated, site of the body would be a highly beneficial therapeutic technique.

The importance of assessing safety standards on MF exposure and microcirculation/microvasculature should be considered. For instance, if an individual was taking medication to control hypotension and a particular MF was known to lead to vasodilation, it may not be in the best interest of the individual to be exposed to the field. Additionally, it may be a worthwhile effort to assess the effects of strong MF exposure, for example, during an MRI scan, on microcirculation. In functional magnetic resonance imaging (fMRI) of brain activity, use of the blood oxygen level dependent (BOLD) signal is common. The differences in magnetic properties of oxygenated and de-oxygenated hemoglobin, mainly within the microvasculature, are used to produce a signal. When fMRI is used to measure related changes in blood flow, there is a possibility that the MFs themselves are causing, confounding, or contributing to, the change. It is largely assumed that such non-invasive imaging techniques are simply measuring blood flow, not altering it. However, reports have been made suggesting that this may not be the case. BBB permeability in rats was increased for 1 h after a 23 min MRI scan at 0.15 T (SMF) [Prato et al., 1990]. Similarly, increased BBB permeability was seen in rats exposed to a clinically relevant MRI procedure: a 1.5 and 1.89 T SMF [Prato et al., 1994]. Certain changes in the radiofrequency and gradient field caused a decrease in BBB permeability. Clearly, it should not be assumed that the MFs encountered during a MRI scan have no other effects on the body. Optical imaging techniques, such as near-infrared spectroscopy, orthogonal polarization spectroscopy, ultrasound Doppler, and Doppler flowmetry should possibly be considered as alternative methods to MRI when possible.

There are a number of potential reasons for the variation in the reports of MF effects on microcirculation and microvasculature. The reviewed studies vary in terms of a number of factors. For instance, some studies measure perfusion during exposure; others, after exposure; and some, during both periods. Discrepancy between studies could be affected by this variable. Furthermore, the duration of exposure and type of MF exposure are no doubt confounding variables. In addition, various anesthetics and organs have been used in the current experiments. This is likely to contribute to the observed differences as reported in the literature.

There are a number of recommendations for future studies. Investigation into the effects of MFs on microcirculation and microvasculature is relatively new and studies are scarce. As a result, limited data is available. For results to be widely accepted, more replication of current studies by independent research groups is needed to validate obtained results. At present, there is controversy within the literature and this tends to weaken the effect of positive findings. Much of the skepticism surrounding the therapeutic action of MF exposure is a result of the uncertainty of the implicated physiological mechanisms. Studies aimed at the cellular level will add more clarity and merit to current results. Further investigation into the possible role of NOS, guanylyl cyclase, endothelium-derived hyperpolarizing factor (EDHF), and Ca^{2+} is needed. In addition, studies that reported a MF effect on microcirculation might simultaneously investigate potential cellular markers of the MF mechanism.

Another recommendation would be to take perfusion measurements during the exposure. In some experimental set-ups, it is difficult to take accurate measurements during the MF exposure due to interference of signals. In a number of the studies cited in this review, perfusion measurements occur post-MF exposure. More measurements during exposure may provide helpful information as to when a biological effect occurs. Research involving the effects of anesthetics on blood flow and blood vessels might also be important and will add further insight into the precise mechanisms behind MF exposure. It may be useful to test a MF effect using different anesthetics and determine whether there are any differences in results. Future investigation might also address the potential microcirculatory effects of MRI.

Broad classification of results may help delineate where, how, and why some studies report positive findings and others report negative findings. The

TABLE 3. Summary of MF Effects on Perfusion and Blood Pressure

Increased perfusion or blood pressure	Decreased perfusion or blood pressure	Biphasic	No effect
Xu et al. [2001]			
		Okano et al. [1999]	
		Okano and Ohkubo [2001]	
	Okano et al. [2005b][a]		
		Ohkubo and Xu [1997]	
Okano and Ohkubo [2003a][b]			
		Okano and Ohkubo [2005a]	
	Okano and Ohkubo [2003b][a]		
Okano et al. [2005a][c]			
		Morris and Skalak [2005]	
			Mayrovitz et al. [2001]
	Okano and Ohkubo [2005b][a]		
			Mayrovitz et al. [2005]
Gmitrov et al. [2002]			
Gmitrov [2004]			
	Mayrovitz and Groseclose [2005]		
Ichioka et al. [1998]			
	Ichioka et al. [2000]		
			Schuhfried et al. [2005]
Smith et al. [2004]			
	Ueno et al. [1986]		
Miura and Okada [1991]			
Mayrovitz and Larsen [1995]			
Mayrovitz and Larsen [1992]			
Huber et al. [2002]			
			Haarala et al. [2003]
Monfecola et al. [2003]			

[a]Initial state of subjects: genetically hypertensive rats.
[b]Initial state of subjects: pharmacologically induced hypertension.
[c]Initial state of subjects: pharmacologically induced hypotension.

TABLE 4. Summary of MF Cellular Effects Related to Perfusion

Increased nitric oxide activity	Decreased nitric oxide activity	No change in nitric oxide activity	Other cellular effects
		Mnaimneh et al. [1996]	
			Okano and Ohkubo [2003b][a]
		Okano et al. [2005a][b]	
	Okano et al. [2005b][a]		Okano et al. [2005b][a]
		Okano and Ohkubo [2005a][c]	
			Cañedo-Dorantes et al. [2002]
Okano and Ohkubo [2005b][a,d]		Okano and Ohkubo [2005b][a]	
			Ruggiero et al. [2004]
			Roland et al. [2000]
			Yen-Patton et al. [1988]
Yoshikawa et al. [2000]			
			Weber et al. [2004]
Noda et al. [2000]			
		Kim et al. [2002]	
			Tepper et al. [2004]
			Ottani et al. [1988]
			Williams et al. [2001]
			Greenough [1992]
Miura et al. [1993]			Miura et al. [1993]

[a]Initial state of subjects: genetically hypertensive rats.
[b]Initial state of subjects: genetically hypotensive rats.
[c]Initial state of subjects: pharmacologically modulated blood pressure.
[d]SMF applied with nicardipine.

potential benefit of this line of research warrants clarification of current findings, as well as further investigation.

CONCLUSIONS

A review of the literature involving the effects of MFs on microcirculation and microvasculature indicates that nearly half of the cited experiments (10 of 27 studies) report either a vasodilatory effect due to MF exposure, increased blood flow, or increased blood pressure. Conversely, three of the 27 studies report a decrease in blood perfusion/pressure. Four studies report no effect. The remaining ten studies found that MF exposure could trigger either vasodilation or vasoconstriction depending on the initial tone of the vessel. For a summary, please refer to Table 3.

In terms of cellular effects of MFs related to perfusion, four of a total of 19 studies report an increase in NO activity as a result of MF exposure (one of these studies used a model with an altered vessel state prior to exposure); one found a biphasic effect; five found no effect. Nine studies report vascular development effects (seven report increased angiogenesis, two report decreased angiogenesis). Other cellular effects are reported in three studies. For a summary, please refer to Table 4.

Clearly, this is an area of research that would benefit from increased investigation. There are many therapeutic applications of locally increased blood flow. It is suggestive that MFs do have the potential to modify microcirculatory perfusion, however, this statement is far from proven.

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