20-kHz ultrasound at 100 W/cm^2 for 60 minutes. This was confirmed in pigs (100 to 140 lb) (33). Transdermal delivery of macromolecules with conserved biological activity was confirmed with ultrasound-induced transdermal delivery of low-molecular-weight heparin (9), demonstrating measurable systemic anti-Xa activity.

In summary, low-frequency ultrasound is able to overcome the skin barrier and could ultimately contribute to valuable therapeutic devices. The extent of enhancement is greater with passively low-penetrating drugs, suggesting that ultrasound interacts with the lipid bilayers of the SC (see Section 5.1) (22). Another field of application for ultrasound-induced skin permeability is the noninvasive quantitative assessment of blood concentration of glucose using reverse skin permeability of glucose (34). After the exposure of the skin of diabetic patients to 20-kHz ultrasound at 10 W/cm^2 for two minutes (50% duty cycle), fairly good correlation was found between glucose concentrations found in extracted fluids and in blood (35) using a vacuum pump to extract dermal interstitial fluid.

43.4 MECHANISM OF ACTION OF ULTRASOUND ON TRANSDERMAL TRANSPORT

The main modes of action of ultrasound-enhanced transport can be briefly summarized as follows: the propagation of ultrasonic waves in a medium induces two main physical consequences, i.e., heating and cavitation. These mechanisms are linked, as cavitation provokes local heating (36). Moreover, cavitation itself can create violent microjets that can dramatically affect adjacent material as metal, and in the present case the SC. Overall the consequence is an increase in skin permeability by increasing fluidity of intercellular lipids and by partial removal of intercellular fluid and possibly some corneocytes, resulting in enlarged intercellular spaces and in the creation of aqueous channels though the SC that can persist after the end of sonication.

43.4.1 Heating

Several phenomena explain the increase in temperature within and at the skin surface exposed to ultrasound. Increase in temperature may be excessive, and it is possible to use an aqueous gel, which decreases reflection, or to use an ultrasound-pulsed mode or a low focused ultrasound wave, which decreases energy density, and to decrease the length and/or the intensity of the sonication.

43.4.1.1 Heating at the Skin Surface

Using 1-MHz ultrasound, Miyazaki et al. (37) showed a rise of 6°C for a fairly low intensity of 0.25 W/cm^2 and 12°C for an intensity of 0.75W/cm^2. Moreover, despite the use of a cooling coil, an 11°C increase occurred in the donor compartment using 1-MHz ultrasound in continuous mode for 4 hours (38). We obtained increases of 15°C to 30°C at intensities ranging from 1 to 3 W/cm^2 (39). Moreover, when heating with an electric resistance, we obtained an equivalent increase in percutaneous flow (Figure 43.2). Our findings obtained with a cooling system did not show any significant increase in percutaneous diffusion rates of various molecules with molecular weight of 138 to 781 Da (azidothymidine, digoxin, hydrocortisone, mannitol, estradiol, salicylic acid) (40, 41). Increase in temperature is thus one of the major factors that can explain the increase in percutaneous absorption in the frequency range from 1 to 3 MHz and in continuous mode. However, a threefold increase was observed with a larger molecule, vasopressin V-2 antagonist (molecular weight 1014 da) (42), demonstrating that heating is not the only mechanism of action of medium frequency.

Using lower-frequency ultrasound (20 kHz, 10 to 30 W/cm^2) and monitoring the temperature, percutaneous flow of hydrocortisone was quadrupled through cellulose membranes and the temperature was increased threefold (25°C to 75°C), whereas the diffusion flux measured was close to that of controls at similar temperatures (43). By contrast, using lower intensities on hairless rat