Imaging of physiologically evoked responses by electrical impedance tomography with cortical electrodes in the anaesthetized rabbit

D S Holder, A Rao and Y Hanquan

Department of Physiology, University College, Gower Street, London WC1E 6BT, UK

Abstract. The purpose of this study was to determine if electrical impedance tomography (EIT) could be used to image impedance changes of several per cent over tens of seconds, known to occur during evoked activity of the cerebral cortex. A ring of 16 electrodes was placed on the exposed superior surface of the brain of anaesthetized rabbits. EIT images were acquired every 15 s using a Sheffield Mark 1 EIT system. During periods of 2.5–3 min of intense photic stimulation of both eyes or electrical stimulation of a forepaw, reproducible impedance decreases of 4.5±2.7% and 2.7±2.4% (mean±SD) respectively occurred in appropriate cortical areas, with a time course similar to the period of stimulation. They were accompanied by adjacent smaller impedance increases. The decreases are probably due to increased blood flow and temperature; the cause of the adjacent increases may be a shadowing artefact of the reconstruction algorithm or due to physiological shrinkage of the extracellular space. This demonstrates, for the first time, that such small changes may be imaged under optimal conditions. These results are encouraging to the prospect that EIT may eventually be suitable for imaging evoked responses or epilepsy in human subjects.

1. Introduction

Electrical impedance tomography (EIT) has the potential for imaging a variety of different processes in the brain, at frequencies of some tens of kHz used currently by single-frequency imaging systems. These include impedance changes of tens of per cent during cerebral ischaemia or cortical spreading depression, of several per cent during epilepsy or physiologically evoked responses over tens of seconds, or even much smaller changes of about 0.01% over milliseconds during action potential related activity in the cortex (Boone 1995; see Holder 1993a for a review). Until recently, the evidence for such changes was all from single-channel impedance measurements made with cortical or intracerebral electrodes. Recently, EIT images of the largest of these changes—cerebral ischaemia (Holder 1992) and cortical spreading depression (Boone *et al* 1994)—have been obtained using a ring of cortical electrodes placed on exposed cerebral cortex.

The mechanism of these changes is well established in the case of both the large changes, namely cell swelling and consequent decrease in the extracellular space (Hansen and Olsen 1980), and opening of voltage-sensitive ion channels during neuronal depolarization (Boone 1995). The nature and causes of impedance changes during physiologically evoked responses is far less clear. Cerebral impedance decreases of several per cent, lasting some tens of seconds, have been observed during physiologically evoked activity, such as exposure to milk or of a female to a male cat (Adey *et al* 1962) or direct electrical stimulation (Aladjalova 1964). To our knowledge, no measurements of cerebral impedance have been made during repetitive evoked responses due to stimulation of the visual, auditory

or somatosensory systems. Possible mechanisms include mild degrees of cell swelling with a consequent decrease in the extracellular space, causing an impedance increase at frequencies below 100 kHz or so, or increased blood flow, blood volume or temperature, which will each cause an impedance decrease.

The eventual use of electrical impedance tomography of the head would preferably be for imaging of pathological or physiological events in the brain in a non-invasive way, with the use of scalp electrodes. EIT imaging work so far has been restricted to measurement directly on the cortex because existing reconstruction algorithms cannot produce adequate images of the brain when scalp electrodes are used, because current is diverted by the highly resistive skull (Holder 1993b). We are currently designing and testing a portable system with flexible drive configuration and specially adapted reconstruction algorithm which may overcome these problems (Cusick *et al* 1994, Bayford *et al* 1996).

The purpose of this study was to see if reproducible EIT images could be produced during physiologically evoked responses. Specifically, we intended to establish if reproducible impedance changes occurred, if they could be distinguished from baseline variability, and if they led to reproducible EIT images. Although the eventual intended application is for imaging through the skull with scalp electrodes, this study was intended as a first step. Measurements were therefore made under what seemed likely to be optimal conditions: a ring of 16 spring-mounted electrodes was placed directly on the exposed cortical surface in anaesthetized rabbits and a well established EIT system, the 'Sheffield Mark 1' (Brown and Seagar 1987), was used, which operates at a single frequency of 50 kHz. Difference images were produced by taking a reference image at rest and comparing further images taken every 15 s over a period of intense continual stimulation lasting about 3 min. An advantage of the preparation chosen is that the exposed superior surface of the rabbit brain is almost flat. As impedance changes may be expected to occur mainly in the cerebral cortex, the anatomical arrangement is therefore largely two-dimensional. It therefore seemed to be tractable from an imaging point of view, as the available Sheffield reconstruction algorithm assumes that the imaged object is two-dimensional.

The findings are that it was possible to image the relatively small impedance changes which occurred during evoked activity; they were a similar size to those expected from previous single-channel studies in the literature. The direction of the predominant impedance change was a decrease in the area expected on physiological grounds. A surprising finding was that each area of decrease was usually accompanied by an adjacent area of impedance increase. Possible reasons are discussed in the final section.

2. Methods

Eight male adult New Zealand White rabbits (3.5–4 kg) were anaesthetized with 0.5–1.0% halothane and in a 70%/30% nitrous oxide/oxygen mixture after induction with 0.3 ml kg^{-1} intramuscular Hypnorm (Fentanyl/Fluanisone, Janssen Animal Health) and 2 mg kg^{-1} subcutaneous diazepam. Animals were paralysed with pancuronium bromide and artificially ventilated. The superior surface of the cerebral cortex was exposed by making a circular craniotomy, 20 mm in diameter; the dura mater was cut away to reveal the pia mater. A circular array of 16 Ag/AgCl spring-mounted ball electrodes, each about 1 mm in diameter (figure 1), was placed on the surgically exposed dorsal surface of the cortex (covering most of the occipital, parietal and frontal cortex). Care was taken to stop any bleeding from the bone or scalp, and exposed cortex and electrodes were covered with liquid paraffin to prevent drying. Common-mode, evoked response reference, and earth electrodes were inserted subcutaneously into the neck. The earth electrode was connected to earth via a

series 10 kΩ resistor, so that the common mode feedback system of the Sheffield Mark 1 system could continue to operate. Arterial blood pressure (BP), end-tidal CO_2, pH and rectal temperature were controlled.
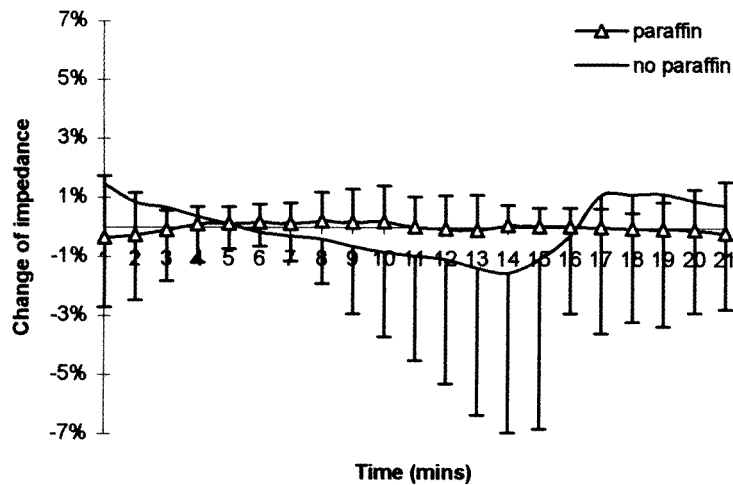

Figure 1. The effect of liquid paraffin on baseline fluctuation in EIT images. Values plotted at each time interval are the mean and SD of all pixels in any one EIT image. Data from two consecutive baseline records, with and without liquid paraffin, in the same animal.

EIT data was collected using a Sheffield Mark 1 APT system (IBEES, Sheffield), with an applied current of 1 mA at 50 kHz. Images were averaged for 12 s, and collected every 15 s, over a total period of 10–20 min. Evoked potentials were collected periodically with a Medelec Sapphire (Medelec Ltd, Woking, Surrey, UK) using four adjacent of the 16 EIT electrodes over the relevant area. Sensory evoked potentials (SEPs) were produced with electrical stimulation of the median nerve at either forepaw with a 0.1 ms square wave, three times supramaximal, delivered at 5 Hz for 3 min. Visual evoked responses (VERs) were evoked by photic stimulation to both eyes, delivered at 10 Hz for 2.5 min.

3. Results

3.1. Baseline drift and variation in EIT images

The magnitude of the evoked response impedance changes was only a few per cent. This is relatively near to baseline fluctuations in impedance. The latter could be reduced to approximately one per cent by care to avoid any bleeding, maintenance of vital parameters, and the applications of liquid paraffin to the exposed cortex (figure 1). In order to ascertain if changes in systemic blood pressure affected the EIT images, the systolic blood pressure was varied between 50 and 140 mm Hg in steps of 10 up to 40 mm Hg by venesection or infusion of warmed physiological saline ($n = 8$ in two rabbits). There were no mean changes greater than baseline variability of 2%, and no consistent impedance changes in any particular region of the image.
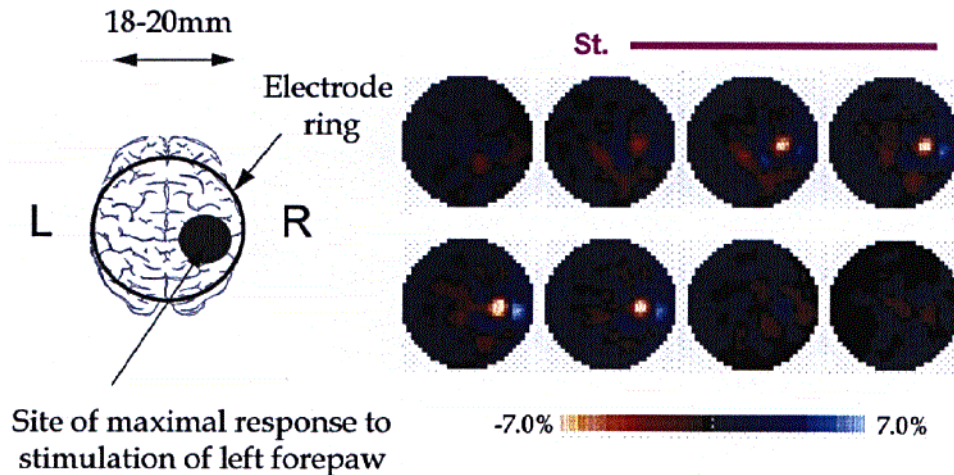
Figure 2. Example of EIT images during electrical stimulation of the left forepaw. EIT images every 75 s. Stimulation period of 3 min indicated by the horizontal line.
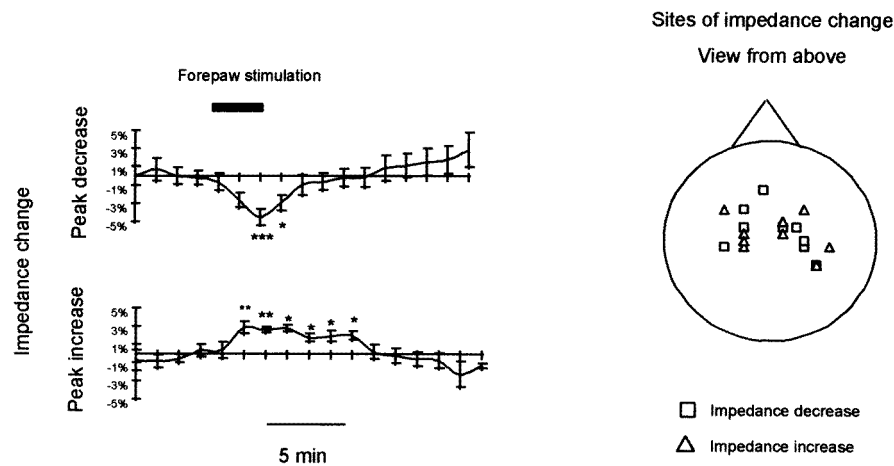

Figure 3. Summary data for changes in EIT images during somatosensory stimulation. The traces show mean $\pm$ SE of the peak impedance decreases or increases ($n = 9$ in three animals; four right and five left forepaw). The diagram shows the positions of these changes: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

3.2. EIT images during somatosensory evoked responses

During median nerve stimulation, in all animals, there were consistent predominant decreases in the cortical impedance in the contralateral somatosensory area of $4.5 \pm 2.7\%$ (mean $\pm$ SD, $p < 0.001$, $n = 9$ in three animals). The decreases were usually accompanied by a small adjacent areas of impedance increase of $2.9 \pm 2\%$ ($p < 0.01$) (figures 2 and 3). The changes commenced about 30 s after the onset of stimulation, and lasted about 4 min before returning to baseline. The mean BP increased on stimulation by 15 ± 5 mm Hg. The SEPs were typically 30 μV in amplitude, with latencies of P1 13.8 ± 1.5 and N1 32.8 ± 3.0 ms ($n = 5$ in three animals, nomenclature as Colin *et al* (1980)) (see figure 6).
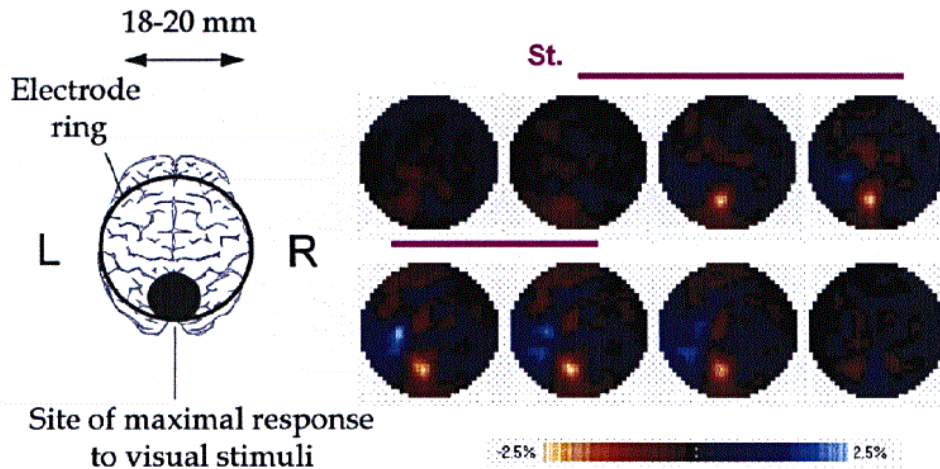
Figure 4. Example of EIT images during visual stimulation. EIT images every 0.5 min. Stimulation period of 2.5 min indicated by the horizontal line.
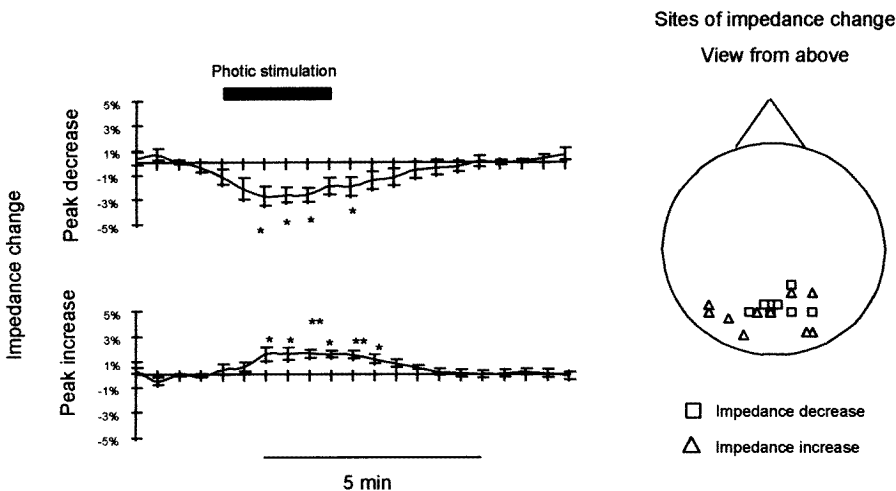

Figure 5. Summary data for changes in EIT images during visual stimulation. The traces show mean $\pm$ SE of the peak impedance decreases or increases ($n = 10$ in five animals). The diagram shows the positions of these changes: $*P < 0.05$; $**P < 0.01$.

3.3. EIT images during visual evoked responses

During visual stimulation in all animals, there were again consistent predominant decreases in cortical impedance in the occipital region of 2.7$\pm$2.4% ($p < 0.05$, $n = 10$ in five rabbits). There were also small adjacent areas of impedance increase of 1.7$\pm$1.1% ($p < 0.01$) (figures 4 and 5). These changes commenced about 15–30 s after the onset of stimulation, and lasted about 3–4 min before returning to baseline. There was no significant change in arterial BP.
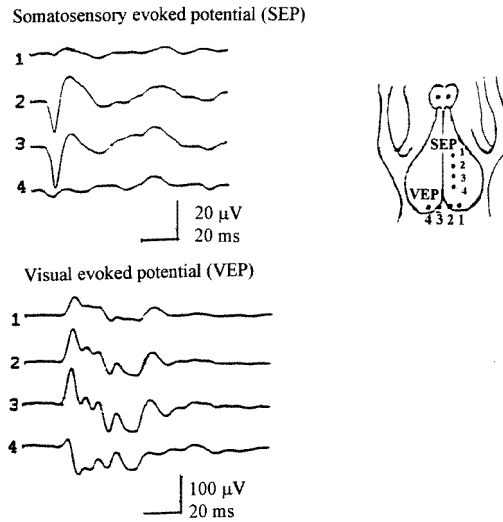
Somatosensory evoked potential (SEP)

20 µV
20 ms

Visual evoked potential (VEP)

100 µV
20 ms

Figure 6. Electrical evoked responses. The upper left diagram shows the results of SEPs recorded during contralateral forepaw stimulation with the four parasagittal cortical electrodes indicated in the diagram. Visual evoked response (lower left) were recorded during binocular photic stimulation with the four occipital cortical electrodes shown.

The VERs were maximal in the same region and typically about 90 μV in amplitude. Initial positivity latency was 25 ± 1.3 ms ($n = 8$ in five animals, nomenclature as Arezzo *et al* (1988)) (figure 6).

4. Discussion

Reproducible changes in impedance do appear to be visible in EIT images during physiologically evoked responses. They occurred with time courses that corresponded to the periods of some minutes of stimulation. The site of these changes was always in the appropriate zone of the cortex—parasaggital contralateral parietal cortex for SEPs, and occipital cortex for VERs (Colin *et al* 1980, Arezzo *et al* 1988)). The magnitude of the changes—a predominant decrease of a few per cent—was similar to those observed during single-channel impedance studies in the limbic system of cats (Adey *et al* 1962).

The principal technical difficulty was to distinguish the relatively small changes from baseline variability. Even after baseline variability was reduced to about 1% from minute to minute by careful improvements to technique, the signal to noise ratio was still only 2 or 3:1. Nevertheless, the impedance changes are statistically significant taken as a group, and it is clearly possible to identify changes in individual series of images (figures 2–5). There is nevertheless some variation in the site of changes within the appropriate cortical lobe (figure 2 and 4). This may be due to physiological variability, slight uncertainties about the precise positioning of the electrodes in relation to cortical anatomy, or physiological variability in the site of maximal change.

A priori, we expected that the changes would be decreases, due to increases in blood volume and temperature known to occur during cortical stimulation, which have a similar time course to those observed in these experiments (Hoshi and Tamura 1993, LaManna *et al* 1989). It is clear that, in keeping with this, the predominant changes are indeed

impedance decreases. However, there also appear to be consistent areas of impedance increase close to those of decrease. The explanation for these is unclear. They could be due to reconstruction artefacts, as impedance changes near the edge can produce ringing artefacts with the Sheffield Mark 1 algorithm (for example Holder and Khan 1994). On the other hand, it is conceivable that in these areas the cortex underwent significant decreases in the extracellular space, which outweighed any temperature and blood volume effects, so causing these impedance increases. A third possibility is that the brain swelled as a result of increased blood volume, and this caused electrode artefacts.

These possibilities were not investigated in this study, whose principal purpose was to determine if these small impedance changes could be detected at all. In our experience with polyacrylamide gels in tanks, which can be made to cause similarly small impedance disturbances, we did not observe similar ringing artefacts (Holder and Khan 1994). However, the geometry was not identical. Future experiments to determine if an algorithm artefact was responsible could include simulation in a tank and local single-channel impedance measurements with a grid of electrodes on the cortex. If the changes were physiological, the likely causes would be cell swelling, causing impedance increases, opposed to increases in temperature, blood flow and blood volume. These could be distinguished by using a laser Doppler flowmeter, thermocouple and, if necessary, direct measurement of the extracellular space using a marker such as tetramethylammonium and an ion-sensitive microelectrode electrode (Hansen and Olsen 1980).

The systemic blood pressure increased during somatosensory, but not visual, evoked responses. It seems unlikely that this contributed to the observed changes, as they were present during VERs as well, and resting studies in which BP was artificially varied did not show similar changes. Nevertheless, it is conceivable that a general rise in BP might affect the images to some extent, as any mild inaccuracy in cerebral autoregulation could lead to a small generalized change in blood volume.

Overall, these results indicate, for the first time, that reproducible impedance changes of a few per cent can be seen in EIT images during functional cerebral stimulation. Successful imaging of these modest impedance changes supports the possibility that the somewhat larger impedance changes during epilepsy (Holder 1993a) may also be imaged by EIT. However, this study was under optimal conditions in an immobile preparation with electrodes on the cortex. The eventual purpose of this work is to develop EIT for clinical use. It remains to be determined whether clinically useful EIT images will be possible with the added difficulties of recording with scalp electrodes in awake ambulant human subjects.

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