Gender and pain – is it an issue?

Correspondence to: Dr Anthony Travers, e-mail: travers@webafrika.org.za

More and more differences in perioperative responses between the sexes in a wide range of areas are being reported in the literature. Many factors including age and co-morbidity are instinctively considered by the anaesthesiologist when considering peri-operative morbidity. The gender of the patient is emerging as a possible indicator of morbidity which needs to be addressed as more data on differences in cardiac physiology and anatomy, gender differences in pain perception, different outcomes following trauma haemorrhage and brain injury are being reported in the anaesthetic literature. Two of the areas that are particularly pertinent to the anaesthesiologist are gender differences in pain perception, and gender differences in the peri-operative presentation and management of ischaemic heart disease.

Gender differences in pain perception

The reporting on gender pain differences is often difficult to interpret because the terms “sex” and “gender” are used interchangeably. According to the Institute of Medicine definition, sex is the “classification of living things, generally as male or female according to their reproductive organs and function assigned by the chromosomal complement”. Gender is “a person’s self-representation as male or female, or how that person is responded to by social institutions on the basis of the individual’s gender presentation”. The relative importance of biological, psychological and social influences on pain reporting and experiences in males and females is a complex field, making objective analysis difficult.

Epidemiology of gender differences in pain

Females report more frequent bouts of pain, more severe pain and longer lasting pain than males with similar diseases. Females have a higher prevalence of pain of musculoskeletal and visceral origin, as well as auto-immune disease related pain. Because females are more likely to visit a doctor than males, pain reporting can be overestimated. The differences in pain perception change as the age of the patient increases and the disease process progresses. To negate these influences many pain related studies are performed on rodents.

Animal studies

Baseline differences

Female rodents have a lower pain threshold in experimental models of hot thermal, chemical, inflammatory and mechanical noiception. In a post-incisional pain model similar to the inflammatory neuropathic pain seen in humans after surgery, no sex differences in pain perception between female and male rodents was shown. Beside baseline differences in pain threshold or response to transient injury, female rodents responded differently to males to non-drug induced anti-nociception. Stress-induced anti-nociception (SIA) is greater in male rodents, whereas in exercise-induced analgesia (EIA) both male and female rats showed decreased sensitivity to morphine-induced analgesia, probably due to increased endogenous β-endorphin levels.

Drug-induced anti-nociception

Opioids

In studies published since 2000, male rodents had a greater response to opioids in 70% of cases. However, 19% of studies showed an equal response between male and female rodents, and 11% indicated greater anti-nociception in females. These discrepancies are difficult to explain, but one plausible explanation can be found in the fact that opioid analgesia is produced by μ, κ or δ receptor stimulation. Male rodents appear to show a stronger anti-nociceptive effect to μ-agonists, whereas females react better to κ-agonists. The biological basis for this μ/κ dichotomy between males and females seems to be supported by genetic studies. Mogil et al.11 discovered that the gene for melanocortin-1 receptor (MC1) mediated κ-opioid agonist anti-

<table>
<thead>
<tr>
<th>Bodily area</th>
<th>Prevalence Female &gt; male</th>
<th>Prevalence Female &lt; male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>Chronic tension</td>
<td>Cluster</td>
</tr>
<tr>
<td></td>
<td>Migraine with aura</td>
<td>Migraine without aura</td>
</tr>
<tr>
<td></td>
<td>Postdural puncture</td>
<td>Posttraumatic</td>
</tr>
<tr>
<td></td>
<td>Cervicogenic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temporal arteritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occipital neuralgia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Odontalgia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Burning mouth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temporomandibular disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trigeminal neuralgia</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arms</td>
<td>Carpal tunnel syndrome</td>
<td>Brachial plexus neuropathy</td>
</tr>
<tr>
<td></td>
<td>Raynaud’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRPS type 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scleroderma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic venous insufficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peroneal muscular atrophy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pinformis syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raynaud’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRPS type 1</td>
<td></td>
</tr>
<tr>
<td>Viscera</td>
<td>Chronic constipation</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td>Bowel</td>
<td>Irritable bowel syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proctalgia fugax</td>
<td></td>
</tr>
<tr>
<td>Oesophagus</td>
<td></td>
<td>Pancreatic disease</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Oesophagitis</td>
<td></td>
</tr>
<tr>
<td>Gall bladder</td>
<td>Postcholecystectomy pain</td>
<td></td>
</tr>
<tr>
<td>Auto-immune</td>
<td>Lupus erythematosus</td>
<td>Reiter’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Fibromyalgia</td>
<td></td>
</tr>
</tbody>
</table>

CRPS = Complex regional pain syndrome
Table modified from Wall and Melzack’s textbook of Pain, 5th Ed.
nociception in female but not in male mice. In the absence of
this gene, male but not male mice demonstrated an enhanced
anti-nociceptive response to κ-agonists. This gene mutation
has no known effect on μ-receptor-induced anti-nociception.
In summary, the more robust response of male rodents to
opioid-induced analgesia may be the result of various factors,
including receptor subtypes.

Other drugs
There is a paucity of information on sex-based differences
in response to other analgesic drugs. The α2-adrenergic drug,
clonidine, produces more analgesia in male rodents after systemic
administration. However, no sex differences have been found
after intrathecal administration. Other drugs such as gabapentin,
cannabinoids and ketamine have shown no sex differences,
while the new anticonvulsant, lacosamide, produced a greater
anti-hyperalgesic response in females.

Human models
The intricate challenges to data collection in humans include
the fact that human responses to pain are influenced by numerous
social, cultural and psychological variables, which are not
necessarily gender specific. A number of pertinent differences
have been found. Women report higher pain severity at lower
thresholds and have less tolerance to noxious stimulation than
males. The greatest disparity in response is for thermal pain,
followed by mechanical pain and deep pressure. Many other
psychological, socio-cultural and physiological variables contribute
to the differences in gender interpretation and experience of
pain.

Biological/physiological factors
Oestrogen plays a central role in pain perception in females.
Women show higher 50% less nausea was observed in
biochemical changes to the female brain. For example, women have
lower response to other analgesics than men. This is probably
due to differential expression of opioid receptors in the brain
regions linked to analgesia.

Advancing age is associated with increased pain threshold and
tolerance, with sex differences becoming insignificant after 40
years of age.

Socio-cultural influences on pain perception
Pain tolerance is highly variable and influenced to a large degree
by gender “norms”. Males who identify strongly with the male
role tolerate more pain than females, while this difference
disappears in males who do not have this belief. Gender roles
also influence pain threshold differences. Males reported less
pain and higher thresholds when tested by a female examiner.
This effect was more pronounced when the examiner was
attractive. Females, on the other hand, report more pain and
lower thresholds with attractive male examiners.

Maladapted pain coping strategies, such as catastrophising,
are associated with poorer tolerance of clinical pain and higher
sensitivity to experimental pain. Women are reported to
catastrophise more than men, and this can account for sex
differences in pain perception. In an attempt to eliminate
psychosocial factors on pain perception as a reason for gender
differences, objective measures of pain have been investigated.
Positron emission tomography (PET) has been used to investigate
regional brain activation after a painful thermal stimulus in
females and males. Mixed results have been reported.
Functional magnetic resonance imaging showed no sex-based
differences in brain activation after matched pain intensity
stimuli.

Non drug-induced analgesia
In the early stages of pain, opioids may produce increased pain thresholds in males. In humans, stress produces no increase in pain threshold in men but does in women. Exercise-induced analgesia shows similar findings with females showing the greatest increase in

Drug-induced analgesia

μ-receptor agonists
Analgesia to μ-receptor agonists
In an experimental thermal pain model, it was found that
morphine is more potent in women than in men (lower C50
value), the onset/offset of morphine is slower in women than
in men, and plasma concentrations of morphine and its metabolites
M-6-G and M-3-G were identical in men and women. This
explains why PCA morphine studies have indicated that women
require more morphine in the first hours after surgery before
analgesia sets in. This means that women require 20 – 30%
larger morphine titration doses when compared with men.
This 2 – 3 times slower onset of action of morphine is possibly
due to slower passage of the drug across the blood-brain barrier.
Interestingly, this disappears in elderly patients. This could
possibly indicate a hormonal effect on the passage of morphine
across the blood-brain barrier.

Some studies have shown an absence of sex differences to μ-
agonists. The reason for these discrepancies is not simple to
explain, but various factors could contribute to the absence of
gender differences:
• Very low doses of opioids on the flat portion of the dose
response curve would not show sex differences.
• Differences in pain models used.
• Absence of reporting on drug plasma concentrations.
• Differences in specific end-points measured and opioids used
different μ-opioids may activate different intracellular G-
proteins.)

Side-effects related to μ-opioid receptor
As a rule of thumb, women experience more side effects and
of greater intensity following μ-opioid receptor agonists than
men do.

i. Nausea and vomiting
In a retrospective study, 50% less nausea was observed in
men than women, after short-term use of opioids (pethidine,
morphine or fentanyl) after minor surgery. In a prospective
study an even larger disparity was found with nausea occurring
in 35% of women versus 3% in men following morphine
administration.

ii. Respiratory depression
There is compelling evidence of the existence of sex differences
in opioid-induced respiratory depression. In a study by
Dahan et al., qualitative and quantitative differences between
sexes with greater respiratory depression in females was
observed. This corresponds with the greater analgesic potency
in women compared with men and probably shares a common
underlying mechanism.

iii. Cardiovascular effects
After low-dose (0.08 mg/kg) intravenous (IV) morphine,
cardiovascular responses between men and women
showed significant differences. Men, but not women,
developed hypertension at this dose, while lower heart
rate values occurred in women. Of more importance, the
cardiovascular response to ischaemic pain was attenuated
in men only.

iv. Subjective effects
Women experience subjective feelings such as a dry mouth,
heavy feeling or “spaced out” feeling more than men. No
difference in motor function between the sexes has been reported.

κ-opioid receptor agonists
Gear et al. showed that nalbuphine, butorphanol and pentazocine
(but NOT morphine) produced better and larger pain relief
in women than in men following dental surgery. Two other studies
failed to demonstrate this gender difference in experimental
pain models (heat pain, pressure pain and ischaemic pain).

None of the latter studies reported on plasma concentrations.
of the drug used, a relevant parameter as t1/2 elimination of pentazocine is greater in women than men.39

Sex differences in κ-opioid analgesia has been linked to the melanocortin-1 receptor gene.32 It has been shown that this gene mediates κ-analgesia in females only. Women, but NOT men, with two or more variant alleles of the MCI gene (all with red hair) show significantly greater analgesia from pentazocine than women without variants or only one variant. Variants are associated with fair skin, freckles and red hair in humans. It is possible that MCI receptors present in the brain are involved in modulation of nociception. Activation of these receptors by endogenous neuromodulators (dynorphin) produces anti-opioid action in females only.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have been shown to influence pain tolerance in human studies, but have no effect on pain threshold. In an experimental pain model, ibuprofen produced an increase in pain tolerance in men, but not in women.33 Although there is a non-sexual inter-individual difference in response to NSAIDs, a lack of response to ibuprofen in female subjects in this study indicates that gender might explain some of these differences. There is no disparity in anti-inflammatory action of NSAIDs, only analgesic efficacy, between men and women. This is probably why this gender difference has not been reported in clinical studies.

In summary, although both animal and human studies report sex and gender differences in pain, the reasons for these differences remain elusive. Possible explanations include molecular and genetic mechanisms, while other factors include psychological, social, cultural and experimental bias. These differences may affect how we treat our patients perioperatively. However, we need more studies to offer clarity on the matter.

Perioperative management of ischaemic heart disease in women

Introduction

In 45% of cases women do not demonstrate chest pain as a presenting symptom of angina.3 Women are 4-5 times more likely to have a false positive exercise test even with normal coronary angiography,39 and 60% of women investigated for chest pain have no stenotic lesions of their coronary arteries despite persistent chest pain.35 Actual ischaemia may thus be missed perioperatively because of theses atypical modes of presentation, which are probably caused by microvascular coronary involvement.

Pathophysiological differences

Hormonal effects

Cyclical hormonal changes (menstrual cycle / pregnancy / menopause) may account for difference in cardiovascular responses between men and women. Oestrogen has anti-atherosclerotic effects, reduces cellular hypertrophy and possesses anti-oxidant and anti-inflammatory properties.36 Oestrogen induces nitric oxide (NO) synthetase gene coding, resulting in vasodilatation and an age matched lower blood pressure in premenopausal women than men.37 Conversely, during menopause, the lack of cyclical oestrogen leads to progressive increases in the incidence of hypertension and pulse pressure. Menopause is also associated with decrease in HDL and an increase in LDL and triglycerides.

In the myocardium, oestrogen receptor signalling inhibits the response to cell injury after myocardial infarction (MI) and attenuates myocardial hypertrophy.40 Oestrogen has also been shown to decrease sympathoadrenal activation. In postmenopausal women, females can develop acute left heart failure with emotional or physical stress in the absence of coronary artery disease (CAD) (Takotsuba Syndrome). These women have higher levels of circulating catecholamines.41 There is an increased incidence of diastolic dysfunction in women compared to men in later life. The causes are multifactorial, but a combination of hypertension, a stiffer aorta and higher total peripheral vascular resistance may explain the higher rate of diastolic failure. Oestrogens receptor-α and oestrogen receptor-β are upregulated by pressure overload. Oestrogen may be beneficial in preserving diastolic distensibility in post menopausal women through effects on renin-angiotensin NO and Ca2+ metabolism in the myocardium.42

Coronary artery physiology in women

Women have smaller coronary arteries and less collateral myocardial circulation than men, leading to an increased incidence of ischaemia when myocardial work is increased. This is independent of body surface area.

Electrophysiology

Baseline heart rate is 4 – 5 beats/min higher in women than in men. Due to a higher baroreflex sensitivity women respond faster to changes in blood pressure, but with less heart rate response to these changes.43

The rate corrected QT interval is prolonged in women and they are more likely to develop ventricular arrhythmias.44 Drugs which prolong the QTc interval are more likely to cause torsade de pointes in women who have a prolonged QTc interval at baseline. Women also develop more episodes of pathological tachycardia, and AV-nodal re-entrant tachycardias than men.

Preoperative risk stratification

Women not only differ in the pathophysiology and symptomatology of CAD, the accuracy of routine preoperative tests for cardiac risk stratification is also different.

Clinical signs and symptoms

Chest pain is not the typical presenting symptom of angina in women, but rather vague symptoms such as fatigue, dyspnoea and lack of energy.36 Older women present with acute coronary syndrome or LV failure after physical or mental stress.

ECG stress testing

The positive predictive value of stress testing is lower in women due to earlier fatigue and the impaired ability to reach target heart rate.45 The diagnostic accuracy is lower in women because their ischaemia is often caused by coronary vasospasm rather than stenosis.36 Almost 50% have normal coronary arteries despite an abnormal stress test, compared with 17% in men. Oestrogen has a digoxin-like effect on the ECG leading to ST segment changes with false positive results.36

These differences make gender-based risk cardiac stratification more prudent, but clear guidelines are not found in the literature. Risk stratification should probably be based on the presence of specific risk factors rather than traditional risk stratification using clinical signs and symptoms, and non-invasive testing. One such approach has identified the following as high risk:46

- Females > 55 years of age
- History of smoking
- Hypertension
- HDL < 40 mg/dl
- Strong family history of CAD

The management of patients with these risk factors is unclear.

Functional capacity in women should be assessed more carefully because women are more likely to have a sedentary lifestyle. A normal EF is not evidence of normal myocardial function, because of the high incidence of diastolic dysfunction in women. New risk assessment paradigms such as inflammatory markers and coronary blood flow reserve i.e. maximal blood flow: blood flow at rest ratio may be included in future risk stratification strategies in women.48

Anaesthetic implications

Traditionally, peri-operative management protocols have been...
based on studies in which either gender was not considered, or in which data for the two sexes was not collected. However, differences in outcomes between men and women have been described after cardiac surgical interventions and high-risk non-cardiac vascular procedures.

Evidence suggests that different pathophysiology and clinical presentation of CAD in women warrants reconsideration of current risk stratification strategies geared to identify men at risk. These differences in physiology are different to that of men: smaller heart size, narrower coronary arteries, increased heart rate, longer cardiac cycle, different autonomic reflexes, different renin-angiotension-aldosterone systems and different response to drugs. These could all affect peri-operative outcome and management.

In future our perioperative management strategies will need to be tailored more specifically to the patient’s gender. This will have definite implications in our anaesthetic practices, ranging from pain management strategies to optimally stratifying and managing peri-operative cardiac risk.

References:

2. Holcroft A, Berkley KJ. Sex and gender difference in pain and its relief. In: Wizeman TM, Pardue M-L. Exploring the biological contributions to human health consideration the patient’s gender. This will have definite implications in our anaesthetic practices, ranging from pain management strategies to optimally stratifying and managing peri-operative cardiac risk.